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THE EFFECTS OF EXPERIMENTAL CHRONIC PASSIVE CONGESTION ON RENAL FUNCTION *

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By experimental methods, the production of varying grades of chronic passive congestion of the kidney has been attempted in order to determine its effect on the urinary and clinical findings, on the excretory capacity of the kidney as revealed by certain functional studies and on the histological structure of the kidney.

In every cardiorenal case which he encounters the physician confronts problems which he is called on to solve. Is the heart or kidney chiefly involved in this case? Which is more responsible for the clinical picture here exhibited? Do permanent and irreparable organic changes exist in the kidneys which preclude the hope of reestablishing a condition of relatively good health, or will the decreased renal function return to normal with the improvement in the cardiovascular system consequent on the enforced confinement to bed? Can chronic passive congestion alone be responsible for the clinical findings? Shall the treatment be directed chiefly to the heart or to the kidneys? Can chronic passive congestion itself interfere to any considerable degree with the excreting capacity of the kidney or can it *per se* institute pathological processes which result in organic and irreparable changes which decrease the capability of the kidney to carry on its work?

By correlating the data obtained from this study with those obtained by utilizing clinically these identical functional tests in a rather extensive series of cardiac, cardiorenal and renal cases, we have attempted to devise some means whereby these problems can be successfully attacked.

HISTORICAL

The effect of partial or complete obstruction to the venous return from the kidney on the urinary picture and the histology of the kidney has been already investigated. Robinson[1] (1843) showed that complete or partial tying off of the renal vein resulted in the appearance of albumin

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1. Robinson: Med. Chir. Tr., 1843, xxvi, 51.

or blood, or both, in the urine, and in the enlargement of the kidney itself. He also performed a one-sided nephrectomy and showed that albumin sometimes appeared in the urine following such an operation, but that by tying the aorta below the level of the renal arteries, together with the above mentioned operation, the appearance of albumin in the urine was more likely to occur. None of Robinson's animals lived more than four and one-half days.

Robinson's work, as well as that of several other investigators, Meyer[2] (1844), Frerichs[3] (1851), Goll[4] (1854), Ludwig[5] (1856), Munk[6] (1864), Erythropel[7] (1865), Stockvis[8] (1867), Weissgerber and Perls[9] (1877), Litten[10] (1879), Posner[11] (1880), Cohnheim[12] (1882), and Heidenhain[13] (1883), has unquestionably established three facts in relation to complete or partial obstruction of the venous return from the kidney for periods varying from hours to a few days.

1. Albuminuria is produced.

2. Hematuria results, particularly if the lumen of the vein be greatly narrowed.

3. Numerous epithelial cells, singly, in groups, or as epithelial casts, appear in the urine.

There is not the same unity of opinion concerning the occurrence of casts in the urine under these conditions; Munk, for example, stating that fibrous and gelatinous casts *(Faserstoff und Gallert)* are never encountered except where nephritis coexists. Burkart[14] also states that following ligation of the renal vein he obtained infarction of the kidney, but no casts in the urine. The consensus of opinion, however, is that casts do occur when the venous return is interfered with, having been described by Frerichs, Erythropel, Weissgerber and Perls, Runeberg[15] and Litten.

Another phase, the effect of obstruction of venous outflow on the quantity of urine excreted, has also been investigated. Paneth[16] (1886) in cleverly devised experiments on anesthetized animals in which known weights were allowed to make traction on a thread, the loop of which

2. Meyer: Arch. f. phys. Heilkunde, 1844, iii, 116.
3. Frerichs: Die Bright'sche Nierenkrankheit und deren Behandlung, 1851, p. 276.
4. Goll: Ztschr. f. rat. Med., iv, 78.
5. Ludwig: Physiologie, ii, 416.
6. Munk: Berl. klin. Wchnschr., 1864, i, 333.
7. Erythropel: Ztschr. f. rat. Med., 1865, xxiv, 217.
8. Stockvis: J. de méd., chir. et pharm., 1867, xlv, 22.
9. Weissgerber and Perls: Arch. f. Pathol. u. Pharmakol., 1877, vi, 116.
10. Litten: Untersuchungen über den hemorrhagischen Infarct, 1879, p. 3.
11. Posner: Virchow's Arch. f. path. Anat., 1880, lxxix, 311.
12. Cohnheim: Allg. Pathol., 1882, ii, 314.
13. Heidenhain: Herrmann's Handbuch der Physiologie, 1883, v, 324.
14. Burkart: Die Harncylinder, Berlin, 1874, p. 46.
15. Runeberg: Deutsch. Arch. f. klin. Med., 1879, xxiii, 225.
16. Paneth: Pflüger's Arch. f. d. ges. Physiol., 1886, xxxix, 515.

was placed about the inferior vena cava above the entrance of the renal vein, or about the renal vein itself, showed that venous congestion *always* caused a decrease in the urinary output. Even the mildest grades of congestion were never associated with a normal or increased amount of urine. Similar conclusions had been drawn by Munk[6] (1864).

Schwarz[17] (1900) states that partial obstruction of the renal vein of one side resulted in a relative polyuria on that side. This he claimed could be obtained with more certainty when the blood was first defibrinated.

De Souza[18] (1900) repeated this work with exactly opposite results even when the blood was defibrinated. He sharply criticized the work of Schwarz, pointing out that the flow of urine from either side, in Schwarz's experiments, was exceedingly small. He concluded that any interference with the return flow of blood from the kidney resulted in lessened urinary output.

Ignatowski[19] (1905) determined the effect on the renal function of ligating one renal vein, the other kidney being left untouched. He showed that the urine for the next twenty-four hours was scanty in amount, poor in chlorid and in urea, contained albumin and blood. He later tied the remaining renal vein, death occurring within a few days.

The work of these various investigators has dealt essentially with the immediate effect (hours to four days) of partial or complete obstruction of the venous return from the kidney on the amount of urine, the presence of albumin, blood and casts in it, and on the histological picture.

The problems with which we deal are: the effects of varying grades of permanent chronic passive congestion (partial obstruction to venous return) on the urinary picture, on the functional capacity of the kidney as revealed by functional studies, on the kidney histologically, and on the general condition of the organism elsewhere.

METHODS

The method utilized for the production of chronic passive congestion of the kidney consisted briefly of the application of constricting bands about the renal veins or about the vena cava above the entrance of the renal veins. The bands were obtained by cutting sections approximately 1 cm. in length from ordinary Coudé catheters which were sterilized by boiling for a period of two or three minutes.

The dog's abdomen was opened aseptically. The vessel about which the band was to be placed was isolated and thoroughly freed from the surrounding tissue. The section of catheter was slit longitudinally, opened, flattened out, and grasped between the blades of an artery forceps in such a manner as to prevent it from curling back into its original shape.

17. Schwarz: Arch. f. Physiol. u. Pathol., 1900, xliii, 15.
18. De Souza: Jour. Physiol., 1900, xxvi, 139.
19. Ignatowski: Compt. rend. Soc. de biol., 1905, lviii, 130.

The band was slipped under the isolated vessel and grasped on the other side with forceps. By careful manipulation it was allowed to curl back into its original shape, enclosing the vessel within its lumen. Heavy silk ligatures were then tied about it, in the center and at either end, holding it firmly in place. The degree of congestion produced was controlled by the caliber of the band utilized, by one-sided nephrectomy, and by ligating or leaving untouched the vessels concerned in the collateral circulation of the kidney. The dog was then allowed to recover from the anesthesia and was placed in an appropriate metabolism cage for immediate observation.

After a series of functional studies the animal was turned loose until such a time as another series was wanted. Repeated observations at periods of days or weeks were made on the urine and on the renal functional capacity. Finally the dogs were killed and the kidneys studied from a pathological point of view.

We have in this manner attempted to create conditions simulating as nearly as possible those existing in cases of cardiac decompensation. In clinical cases there is stasis which undoubtedly interferes with the free flow of blood from the kidney. Since the heart action in cases of decompensation is weakened, there must exist a disproportion between the driving force on the arterial side and the outflow on the venous side. And while our experiments have been conducted on animals with normal hearts, the constriction of the vein leads here also to a disproportion between the inflow and the outflow. Therefore, we may assume that the conditions of our experiments actually resemble the conditions encountered clinically[20] as closely as experiments with animals with normal hearts will permit.

The functional tests used in this connection were essentially five, e. g., phenolsulphonephthalein, lactose, salt, potassium iodid and water. In our earlier studies the excretion of certain other dye substances was studied in certain cases as was also the glycosuria following the injection of phloridzin. It became apparent early that nothing was to be gained from the continued use of indigo carmin and carbol fuchsin (rosanilin) in this connection,[21] inasmuch as they were excreted roughly in propor-

20. We are aware that in certain respects differences do exist. Although in the pressure exerted a similar relative disproportion exists in the two conditions, naturally where the *vis a tergo* is normal the absolute pressure may be greater. Furthermore, there is a possibility that the insufficient oxygenation of blood generally, in broken compensation, plays a rôle in determining renal function. We do not think so much in this connection about the diminished oxygen supply to the kidney as of the possible toxicity of the waste products of other organs which suffer from lack of oxygen, affecting renal function.

21. Personal observations to be published later. For discussion of these tests, see also publication of Rowntree and Geraghty, Jour. Pharm. and Exper. Therap., 1910, i, 579.

tions paralleling the excretion of phthalein. The use of the indigo carmin was discarded, since its colorimetric properties are not well adapted to accurate quantitative work. Both drugs are excreted much more slowly than is the phthalein. The glycosuria following the administration of phloridzin seems to bear some relation to the excretion of lactose under similar conditions; e. g., glycosuria is prolonged. Phloridzin glycosuria, however, is exceedingly variable under any conditions and it was considered more advantagous to use only lactose, on which greater reliance can be placed.

In some of our later experiments observations were made on the urea and nitrogen content of the blood, which has been considered by Prevost and Dumas[22] (1821), Christison[23] (1834), Bright[24] (1836), Frerichs[25] (1851), Ascoli[26] (1901), Strauss[27] (1902), Müller[28] (1904), Obermeyer and Popper[29] (1911), Hohlweg[30] (1911), Widal[31] (1911), von Noorden[32] (1907), to be materially augmented wherever marked decrease in the excretory capacity of the kidney exists.

A brief description of these various tests, together with the technic, follows:

The Phthalein Test was used according to the original technic described by Rowntree and Geraghty.[33] One cubic centimeter of a phenolsulphonephthalein solution containing accurately 6 mg. was injected under antiseptic precautions into the lumbar muscles of the dogs, which were then placed in metabolism cages. A catheter was passed at the expiration of an hour and ten minutes and the total urine for this period collected. The urine was made distinctly alkaline, diluted to 1 liter, and the amount of drug present determined by the use of our[34] modification of the Autenrieth-Königsberger colorimeter. In our previous work with this test we have already determined that the output for normal dogs is 50 per cent., or more, for this period.

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22. Prevost and Dumas: 1821. Cited by Schöndorff, Pflüger's Arch. f. d. ges. Physiol., 1899, lxxiv, 307.
23. Christison: On Granular Degeneration of the Kidney, 1834.
24. Bright: Guy's Hosp. Rep., 1836, i, 358.
25. Frerichs: Die Bright'sche, etc., 1851.
26. Ascoli: Pflüger's Arch. f. d. ges. Physiol., 1901, lxxxvii, 103.
27. Strauss: Die chronischen Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung, 1902.
28. Möller: Verhandl. d. Deutsch. path. Gesellsch., 1904-5, vii-ix, completing No. 80.
29. Obermeyer and Popper: Ztschr. f. klin. Med., 1911, lxxii, 332.
30. Hohlweg: Deutsch. Arch. f. klin. Med., 1911, civ, 216.
31. Widal: Bull. et mém. Soc. méd. d. hôp., Paris, 1911, Series 3, xxxii, 627.
32. Von Noorden: Metabolism and Practical Medicine, 1907, ii, 486.
33. Rowntree and Geraghty: Jour. of Pharm. and Exper. Therap., 1910, i, 579.
34. Rowntree and Geraghty: THE ARCHIVES INT. MED., 1912, ix, 284.

The lactose, potassium iodid, salt and water tests, which have received a thorough study at the hands of Schlayer[35] and his coworkers in relation to the renal function in experimental acute toxic and vascular nephritides, and also in relation to nephritis as it exists clinically, were applied to this study of the renal function in chronic passive congestion. Schlayer's technic was adhered to as closely as possible.

Lactose was shown by Voit[36] to be excreted quantitatively by the kidneys following subcutaneous or intravenous administration. De Bonis[37] showed that lactose was excreted by the glomeruli. Schlayer therefore adopted it as a means of determining the functional capacity of the glomeruli in various forms of experimental nephritis and in the nephritides encountered clinically. He admits that its excretion is delayed in passive congestion, and therefore in his clinical studies he avoided cases which exhibited cardiac inefficiency. He considered delay in lactose excretion to be evidence of functional derangement of the vascular system. Since it is a substance foreign to the body and consequently not subjected to the many extrarenal factors which influence the excretion of water, he places his chief reliance on this test for information concerning the vascular functional capacity. Schlayer worked with rabbits and administered the lactose intravenously. We have worked with dogs, injecting it into the lumbar muscles.

Since De Bonis does not claim that lactose is not excreted by way of the tubules but merely that it is well excreted by the glomeruli, we thought that the frog's kidneys might furnish valuable information in regard to the mechanism of the excretion of lactose. Nussbaum[38] showed that the tubules in the frog's kidney are supplied by the renal-portal system which is entirely separate and independent of the arterial supply of the glomeruli. This work has been confirmed by Beddard,[39] Cullis,[40] and Rowntree and Geraghty.[33] An attempt was, therefore, made to see if the frog's kidney could excrete lactose in the absence of the glomerular system.

Large male frogs, *Rana catesbiana*, weighing about 300 gm., were pithed, their abdomens opened by long incisions on each side of and parallel to the anterior abdominal vein. The left kidney was exposed and all the arterial connections severed by means of the Paquelin cautery

35. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xcviii, 17; 1911, ci, 333; and Schlayer, 1911, cii, 311.

36. Voit: Deutsch. Arch. f. klin. Med., 1897, lviii, 545.

37. DeBonis: Giorn Internat. d. sc. med., 1907, xix, 446, 451.

38. Nussbaum: Pflüger's Arch. f. d. ges. Physiol., 1878, xvi, 179; xvii, 580.

39. Beddard: Jour. Physiol., 1902, xviii, 20; see also Bambridge and Beddard: Jour. Physiol., 1906, xxiv; Proc. of Physiol. Soc. p. ix, and Biochem Jour., 1906, i, 255.

40. Cullis: Jour. Physiol., 1906, xxxiv, 250.

as suggested by Beddard. A cannula was then inserted into the anterior abdominal vein and a small glass cannula inserted into the left ureter. Protocols will indicate the course of the experiment and the results obtained.

PROTOCOLS OF EXPERIMENT

I. Ringer's solution was perfused from a Mariotte flask through the renal-portal system under a pressure of 35 cm. of water. Perfusion for fifteen seconds every three minutes was begun at 12:30 and continued until 12:50, no urine being secreted. At this time sufficient sulphonephthalein to make a 1 per cent. solution was added to the Ringer's solution and perfusion continued until 1:30 p. m., still no urine being excreted. Sufficient urea and lactose were then added to make a 1 per cent. solution of the former and an 8 per cent. solution of the latter and the perfusion continued. At 1:45 the urinary flow started, phthalein making its appearance but lactose being absent. At 2 p. m. sugar was recovered from the urine excreted.

II. Ringer's solution was perfused from a Mariotte flask through the renal portal system under a pressure of 35 cm. of water. Perfusion for fifteen seconds every three minutes was continued from 3:30 p. m. to 4 p. m. without any flow of urine. At 4 p. m., sufficient lactose to make a 0.5 per cent. solution was added to the perfusing fluid. Urinary flow started at 4:15 p. m. A trace of sugar was in the urine at 4:45 p. m. Phthalein (6 mg.) and sufficient urea to make a 2 per cent. solution were added to the perfused fluid at 5 p. m. At 5:30 p. m. the urine contained sugar and phthalein.

The kidney was perfused at 5 p. m. with a saturated solution of Prussian blue, immediately removed and placed in absolute alcohol. Serial sections were made but no blue found in the glomeruli.

From this it is seen that the frog's urinary tubules are capable of excreting lactose. We feel, therefore, that sufficient proof has not been presented that lactose is excreted by the glomerular system entirely.

From a repetition of Schlayer's work on acute toxic nephritis and our own, as well as his experience with its use as a functional test clinically, and from the evidence presented in this study, we feel that the mechanism of its excretion differs essentially from that of phthalein, salt, indigo carmin, etc. Throughout this investigation we have used it as Schlayer did as an index of the condition of the vascular function of the kidney, admitting, however, that we need much more information concerning the manner and significance of its excretion.

TECHNIC

Our technic was as follows: 3 gm. of lactose in 15 c.c. of distilled water was injected into the lumbar muscles under aseptic precautions. The animals were placed in metabolism cages, catheterized at the end of four hours, and thereafter every half hour up to eight and nine hours. The total amount of lactose excreted in four hours was determined polarimetrically in a great many instances by the Schmidt and Haenisch instrument, but since the time necessary for total elimination is considered by Schlayer to be of greater importance, we have studied this more particularly. The presence of lactose in the urine has been determined by means of the Fehling and Nylander tests. The total time necessary for complete excretion of lactose under such conditions normally does not exceed six hours.

Potassium Iodid Test.—Potassium iodid was one of the first substances to be utilized in connection with functional renal studies, being introduced by Duckworth[41] in 1867. It appears quickly in the urine following its administration by mouth, Quetsch[42] stating that it appears in nine to eighteen minutes after a 2 gm. dose, Roux[43] thirteen minutes after a 3 gm. dose, and Studeni[44] thirteen to eighteen minutes after a 1 gm. dose. The time required for complete elimination, as stated by different authors, varies markedly. According to Geisler,[45] 6 gm. require twenty-five hours; Roux, 5 gm. require thirty hours; Studeni, 1 gm. requires thirty to thirty-six hours; Anten,[46] 0.5 gm. requires forty hours; Schlayer and Takayasu[47] and Monokow,[48] 0.5 gm. requires forty-eight hours. Schlayer, in his studies, however, did not consider anything less than sixty hours to be a delayed excretion time following 0.5 gm. by mouth.

According to the studies of Schlayer, potassium iodid is excreted by the tubules of the kidney and on it he has placed most dependence in determining tubular functional capacity. Anten[46] showed that the excretion is not hastened by the occurrence of diuresis. It has been claimed by Schlayer and Takayasu[47] that its excretion is not influenced by chronic passive congestion and that it is not delayed in cases of cardiac decomposition, characteristics which, if true, would make it of tremendous importance in differentiating cases of pure passive congestion of the kidney from passive congestion associated with nephritis.

In our studies 0.5 gm. of potassium iodid was administered by stomach tube and its presence in the urine determined by Sandow's[49] test. This amount we have found normally to be excreted within forty-eight hours, but, like Schlayer, we have considered a delayed excretion only that which continues for more than sixty hours.

In certain instances, on account of vomiting, the drug was given directly into the blood by means of an intracardiac injection. Following such administration it is entirely eliminated normally within twenty-four hours.

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41. Duckworth: St. Barth. Hosp. Rep., iii, 216.
42. Quetsch: Berl. klin. Wchnschr., 1884, xxi, 353.
43. Roux: Thèse de Paris, 1890, No. 243. Experiences sur l'elimination des jodures par l'urine.
44. Studeni: Untersuchungen über die physiologische Ausscheidung der Jodpreparate durch den menschlichen Harn. Zürich, 1897.
45. Geisler: Cited by Anten (Note 46).
46. Anten: Arch. f. Path. u. Pharm., 1902, xlviii, 331.
47. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1911, ci, 354.
48. Monokow: Deutsch. Arch. f. klin. Med., 1911, cii, 309.
49. Sandow's method consists of adding 1 c.c. of 2 per cent. sodium nitrite solution and 1 c.c. of 10 per cent. H_2SO_4 to from 10 c.c. to 30 c.c. of urine, followed by the addition of a small amount of chloroform. This is shaken together and allowed to separate into layers, the presence of the iodid being indicated by a purplish-red or violet color in the chloroform.

The Salt and Water Tests.—The excretion of salt following its administration in amounts greatly in excess of that ordinarily taken with the food, is accomplished by the tubules, according to Schlayer. Normally a large amount of salt is excreted by one of two methods. If it is given without extra water it is almost entirely excreted within twenty-four hours, without diuresis, by increased salt concentration in the urine; if given with an excess of water it is excreted partially through increased concentration in the urine and partially through diuresis.

Where vascular injury to the kidney exists we may have the simple administration of salt followed by a marked diuresis, all of the salt being smoothly excreted in twenty-four hours without its percentage content in the urine being at all increased. This is usually associated with a somewhat low and fixed specific gravity and the syndrome is spoken of as "vascular hyposthenuria." Here the inability to concentrate is not due to any incapacity of the tubules to excrete salt, but on hypersensitive vessels which respond to the salt administration with a diuresis. In more severe vascular injury the vessels do not act in the same way, oliguria characterizing the urinary picture. In severe tubular destruction, a urine of fixed low specific gravity is obtained, the quantity of which is not materially affected by the administration of salt and the salt content of which is not augmented by administration of extra amounts of salt because of the inability of the tubules to excrete it. Such a condition is known as "tubular hyposthenuria."

In this study the daily excretion of salt, both as to per cent. and total excretion, was first observed, the animal being kept on a constant diet. An extra 3 gm. of salt were given by mouth and the effect on the percentage content in the urine and on the total salt output for the following twenty-four hours determined. In certain instances, where administration of the salt by mouth produced vomiting, 1.5 to 2 gm. of salt were given intravenously or directly into the heart by an intracardiac injection. The Lütke-Martius[50] method was used throughout in the chlorid determinations.

VARIOUS METHODS OF PRODUCTION OF CHRONIC PASSIVE CONGESTION OF KIDNEYS

In order to obtain passive congestion of the kidneys, bands were placed, by the technic described above, on one or both renal veins, on the vena cava above the entrance of the renal veins, on the aorta below the origin of the renal arteries, while simultaneously vessels concerned in the establishing of collateral circulation were ligatured; the production of hyperemia was attempted by placing a band about the aorta below the

50. Sahli: Diagnostic Methods, 1911, 177.

level of the renal arteries. The urinary picture, functional renal capacity and pathological findings obtained following these various methods are indicated below.

A BAND ON THE VENA CAVA ABOVE ENTRANCE OF RENAL VEINS

The effect of placing a constricting band on the vena cava just above the entrance of the renal veins, without handling the kidneys or interfering in any way with their collateral circulation, is shown in the following protocols:

HOUND BITCH I.—Weight 15 kg.

February 3. Was etherized. A band was placed about the inferior vena cava just above the entrance of the renal veins, constricting the cava to about one-third its normal size.

February 4. Animal is apparently feeling very well, eats and drinks normally and is playful.

February 5 and 6. Urine[51] shows a trace of albumin, a few hyaline and granular casts; no red blood-cells or pus. Phthalein output normal—70 per cent. in an hour. Lactose excretion delayed, 50 per cent. excreted in four hours; positive after eight hours.

February 14 and 15. Wound has healed perfectly. Dog apparently in normal condition.

Urine: Albumin a trace; negative for blood, pus or casts. Phthalein normal, 52 per cent. in an hour. Lactose excretion slightly delayed, 27 per cent. for four hours, still faintly positive at seven hours. Salt well concentrated.

February 27 and 28. Animal appears normal. Phthalein 65 per cent. Potassium iodid, forty-eight hours. Lactose, six hours. 3.7 gm. salt excreted on a 3 gm. intake. Salt concentrated good 1.2 per cent. The kidneys are therefore functionally normal.

April 22 to 24. Animal is normal apparently. Urine shows a trace of albumin, but sediment contains no abnormal elements. Phthalein 60 per cent. Potassium iodid 48 hours. Lactose slightly delayed—seven hours.

May 13. Animal is pregnant. Urine excreted in fair amounts. Specific gravity 1,040, slight trace of albumin. No casts or blood. Phthalein and salt normally excreted while potassium iodid requires sixty hours. Lactose more delayed than at last observation; still strong in urine after eight hours.

June 1. The bitch gave birth to a litter of pups. Her condition was excellent. No functional studies were made.

BITCH II.—Weight 7.2 kg.

January 31. Band placed about inferior vena cava just above entrance of renal veins. Ether anesthesia lasting one hour.

February 1 and 2. Animal in excellent condition, behaves normally. Urine contains albumin ¼ to ½ per cent., shows a few granular casts and epithelial cells. Phthalein output is normal, 60 per cent. Phloridzin glycosuria persisted four hours. Lactose excretion delayed; urine strongly positive for sugar at end of eight hours.

February 5. Excreted 150 c.c. of urine on a 500 c.c. fluid intake. Intake of salt 5.4 gm. with only a trace excreted. Urine shows only a slight trace of albumin and a few hyaline and granular casts.

February 19 to 23. Animal apparently normal. Phthalein 60 per cent. for one hour. Lactose is delayed; urine reacting strongly at end of seven hours. Salt excreted in good concentration, 2 per cent.—4 gm. output on 5 gm. intake. Potassium iodid requires seventy-two hours for excretion.

March 8. Dog has developed distemper. Chloroformed.

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51. All urinalyses here recorded were made on catheter samples.

From these experiments it is evident that a moderate obstruction to the inferior vena cava above the level of the renal veins causes no serious change in the renal function. A persisting mild albuminuria is produced which is associated early with the presence of casts. The urinary output is fair in amount. The excretion of lactose is markedly delayed; salt excretion may be somewhat slow at first, but later is normal. The potassium iodid was delayed in one animal, normal in the other. The phthalein was absolutely normal throughout. That no serious injury to the renal function is produced is evidenced by the subsequent history of the animal. Eventually a practically normal functional picture is obtained, although slight albuminuria persists.

BANDS ON BOTH RENAL VEINS

Bitch III.—Weight 35 kg.

December 19. Moderately tight bands placed on both renal veins.

December 21 and 22. Urine small in amount, shows albumin and numerous red cells but no casts. The phthalein was excreted in a mere trace on the 21st, and 8 per cent. for one hour on the 22d. Only a trace of rosanilin excreted.

December 26. Animal is feeling badly; walks about but does not eat. Vomits after drinking small quantities of water. Wound is infected. Phthalein and rosanilin were injected but no trace of them could be found in urine at end of one hour. Urine is very scanty, containing albumin and blood.

December 28. Found dead. No careful study of the condition of the renal veins as to thrombosis or slipping of the band, etc., was made.

Bitch IV.—Weight 10 kg.

January 22. Bands placed about both renal veins causing marked congestion.

January 23. Animal is exceedingly playful. Phthalein output 52 per cent.

January 25 to 31. Animal in excellent condition. Urine is normal in amount and contains albumin ⅛ to ¼ per cent. On some examinations the sediment contains a few hyaline and granular casts and a few red blood cells while at other examinations sediment is normal. The phthalein is excreted normally, 52 per cent. in one hour. Rosanilin is also well excreted. Potassium iodid is markedly delayed, 100 hours being required for total excretion. Lactose is markedly delayed, while salt is excreted normally—1.4 per cent. and absolute output 5 gm. on a 5.2 gm. intake. The glycosuria following phloridzin is very slightly prolonged.

February 14 and 15. Animal in excellent condition. Phthalein output 65 per cent. Salt excreted well 1.5 per cent. concentration and 6.5 gm. absolute on a 6 gm. intake. Potassium iodid excretion still delayed—eighty hours. Lactose slightly delayed—six to seven hours. Urine plentifully excreted, 500 c.c. on 600 c.c. intake of water. Sediment negative for pus, blood and casts.

February 20. The abdomen was again opened. Both kidneys were seen to be enlarged and markedly engorged. The capsular veins were strikingly enlarged and tortuous. The left kidney was removed for histological study. The band was found in place surrounded by fibrous tissue and the veins not thrombosed.

A BAND ON LEFT RENAL VEIN; RIGHT-SIDED NEPHRECTOMY

A more pronounced grade of congestion was attempted through a right-sided nephrectomy and a band about the vein of the remaining kidney. The effect of such a procedure on the renal function was studied on several dogs, the results appearing in Table 1.

TABLE 1.—EFFECT ON RENAL FUNCTION OF A RIGHT-SIDED NEPHRECTOMY WITH BAND ON LEFT VEIN

Dog	Wt., Kg.	Date 1912	Condition	H_2O, c.c.	Urine				Lactose, Hrs.	KI, Hrs.	Salt			Remarks
					Quantity, c.c.	Sediment	Albumin	Phthalein			In, gms.	Out gms.	Per Cent.	
V	7.9	1/12	.....	...	...	.....	.....	.....	....	.....	...	....	.....	Operation; rt. kidney removed; wt. 30 gm. Moderately tight band on left renal vein. Phloridzin glycosuria 7° on 13th. Indigocarmin 5 per cent. in 1 hr. on 14th. Carbol-fuchsin 11 per cent. in 3 hrs. on 15th. Animal chloroformed. Left kidney showed marked chronic passive congestion. Wt. 50 gm. No venous thrombosis. Peritonitis.
		13	Good	200	120	.....	++	26	....	.....	...	.25	.21	
		14	Depressed	300	270	Many R. B. C. Hyaline and granular casts	+	.....	....	.....	...	.18	.03	
		16	Depressed	...	...	Epith. cells and a few hyaline casts.	.....	6	8°+	24 Intra-cardiac	...	....	.....	
		17	Very sick	200	350	.....	.....	16	....	.....	...	Trace	Trace	
VI	5.4	1/12	.....	...	...	.....	.....	.....	....	.....	...	....	.....	Operation; rt. kidney removed. Moderately tight band on left renal vein. Phloridzin glycosuria 7° on Jan. 13. Carbol-fuchsin 45 per cent. in 3 hrs. on 15. Phloridzin glycosuria 6° on Jan. 15. Indigocarmin 7 per cent. in 2 hrs. Jan. 17. Phloridzin glycosuria 5° on the 29. Carbol-fuchsin 40 per cent. in 3 hrs. on Jan. 29.
		13	Good	300	180	.....	+	25	....	72	...	.41	.23	
		14	Good	250	210	Occasional R. B. C.	+	.....	....	.....	...	.45	.22	
		15	Excellent	300	277	.. ..	.....	90 (2.5°)	8°+	.....	...	....	.....	
		17	Excellent	400	180	.....	.....	30	8°+	.....	...	Trace	Trace	
		1/23-26	Excellent	400	good	Occas. R. B. C. hyaline and gran. casts.	⅛ to ¼%+	.....	8°+	72	3.5	1.8	.5	Chloroformed. Kidney was found to have an accessory renal vein. No marked congestion was found.
		1/29-31	.....	...	...	Hyal. and cell. casts; R. B. C.	⅛ to ¼%	52	8°	72	5.2	3.4	1.3	
		2/9	Excellent	...	...	.....	.....	65	8 +	.....	...	....	.....	
		2/13	Distemper	...	..	.....	.....	.....	....	.....	...	....	.....	

IV	10.0	2/20	.....	...	...	.....	.....	.....	....	.....	...	....	.....	One month previously dog had had bands placed on both renal veins; 2/20/12 left kidney removed. May 24 animal very lively and playful. The right renal vein was tied and animal lived on the collateral venous return.*
		2/21	Good Thin	...	...	.....	.....	.....	....	.....	...	....	.....	
		3/18	.....	...	421	Few hyal. and gran. casts; epith. cells	++	40	8°+	66	4.2	1.6	.39	
		5/13	Excellent	300	300	Blood and pus cells; few red cells	+	55	....	.....	2.6	2.4	.8	
		5/24	Excellent	300	300	.....	+	56	8	60	3.0	2.4	.8	
VII	9.6	1/29	.....	...	...	.....	.....	.....	....	.....	...	....	.....	Two anesthesias as vagina was slit open 3 days previously. Left kidney wt. 34.5 gm. Tight band on right renal vein. Phloridzin glycosuria 4° on Feb. 1.
		2/1	.....	...	70	Few hyal. and cell. casts; few R. B. C.	¼ to ½%	54	8°+	.....	...	....	.....	
		5-6	Good	700	440	Numerous R. B. C. and W. B. C.; no casts; normal	+	50	....	.....	5.4	1.6	.38	
				800	550				....	.....	5.0	1.2	.20	
		3/21-22	Good	500	300	.....	0	75	....	.....	...	....	.....	
		3/30 4/1	Thin	...	...	.....	Trace	60	8°+	48	3.0	2.2	1.1	Injected vital stain. Killed animal. Kidney wt. 62 gm. Band in place; no thrombosis.
VIII	6.0	1/27	.....	...	...	.....	.....	.....	....	.....	...	....	.....	Left kidney removed; tight band on left renal vein. Carbol-fuchsin 35 per cent. after 3° on 29. Phloridzin glycosuria 5° on 30. May 15, renal vein tied. Animal lived on collateral venous return.*
		29	Excellent	...	...	.....	.....	.....	....	.....	...	....	.....	
		31	Good	300	400	.....	⅛ to ¼%	.....	8°+	100	5.2	3.0	.73	
		2/18-23	Good	300	100	.....	.....	80	7°+	.....	...	....	.....	
		4/22	.....			Normal	0	55	6°+	.....	...	....	.....	
		5/8	Good	500	370	.....	+	70	7°	.....	3.0	3.2	.87	

* Described in text.

TABLE 2.—EFFECT ON RENAL FUNCTION OF LIGATING COLLATERAL AS WELL AS RENAL VEINS

Dog	Wt., Kg.	Date 1912	Condition	Sp. Gr.	H_2O, c.c.	Urine						Salt			Remarks
						Quantity, c.c.	Sediment	Albumin	Phthalein.	Lactose	KI, Hrs.	In, Gms.	Out, gms.	Per Cent.	
IX	6.0	3/5	.....	....	...	...	.....	....	....	....	... .	.....	....	.....	Right kidney removed. Wt. 28.5 gm. Moderately tight band on left renal vein; ovarian and lumbar veins ligated.
		6 & 7	Good	1018	700	500	No casts	++	54.0	8°+	48	3.0	3.0	.6	
		9 & 10	Distemper	1012	500	450	.....	....	12.0	....	.....	3.0	.63	.14	
		11	.....	....	...	...	Many red blood cells; no casts	....	Trace	8°+	.....	.....	....	.....	General infection. 12th — found dead. Thrombosis of renal vein. Large subcapsular hemorrhage. Kidney weight 50 gm.
X	6.5	3/18	.....	....	...	...	.....	....	....	....	. .....	.....	....	....	Right kidney weighing 24 gm. removed. Moderately tight band about left renal vein; ovarian, lumbar and suprarenal veins tied. Animal killed—thrombosis of renal vein at site of band. Kidney wt. 40 gm. No peritonitis. Kidney markedly congested.
		19	Good	1032	...	...	Numerous hyaline and granular casts; no blood	+	47.0	7°+	72	.....	....	.....	
		21	Fair	1018	500	400	.....	....	9.0	....	.....	3.2	2.4	.61	
		22	.....	....	...	...	.....	....	7.5	....	.....	.....	....	.....	
		23	.....	1018	500	300	Blood, pus and epith., no casts.	++	11.5	....	.....	.....	....	.....	
		24	. .....	....	...	...	.....	....	11.5	....	.....	.....	....	.....	
		25	Fair	....	...	...	.....	....	15.0	....	.....	.....	....	.....	
		26	. .....	1016	500	670	.....	....	12.0	8°+	60	4.0	1.4	.16	
		28	Very sick	1018	...	...	.....	+	11.0	....	.....	.....	....	.....	
		29	.....	....	...	...	Blood, pus and casts	+	5.0	....	... .	.....	....	.....	

XI	6.0	3/20	.....	....	...	...	.....	....	....	...	.....	.....	....	.....	Right kidney removed. Wt. 24 gm. Moderately tight band on left renal vein. Ovarian, lumbar and suprarenal tied. 28th — found dead.
		21	Good	1047	...	...	Few epith. cells W. B. C.	++	32.0	....	.....	.....	....	.....	
		23	.....	1039	400	300	.....	....	50.0	....	.....	.....	....	.....	Band in place. No thrombosis. Cause of death unknown. Heart and lungs negative. No peritonitis.
		24	Excellent	....	...	...	.....	....	60.0	....	.....	.....	....	.....	
		28	Dead	....	...	...	.....	....	....	....	.....	.....	....	.....	
XV	8.0	4/19	.....	....	...	...	.....	....	....	....	.....	.....	....	.....	Right kidney removed. Left kidney banded fairly tight. Ovarian tied at entrance to renal.
		20	Fair	1024	...	400	Casts, hyaline and granular	++	....	7°+	48	2.0	....	Trace	
		22	Distemper	....	...	...	.....	....	60.0	6°	.....	.....	....	.....	Typical bronchopneumonia; beginning thrombosis of left renal vein. Kidney showed marked congestion and some cloudy swelling.
		26	.....	....	...	...	Occasional cast	0	36.0	....	.....	.....	....	.....	
		27	.....	....	...	...	.....	....	48.0	....	.....	.....	....	.....	
		28	Dead	....	...	...	.....	....	....	....	.....	.....	....	.....	
XII	8.5	3/26	.....	....	...	...	.....	....	....	...	.....	.....	....	.....	Right kidney removed. Wt. 34 gm. Left renal vein tied.
		27	.....	....	few c.c. Anuria	few c.c.	Much blood; hyal., gran. and cellular casts	++	0.0	....	.....	.....	....	.....	
		28	Chloroformed	....	...	...	.....	....	....	....	.....	.....	....	.....	Chloroformed. Kidney 52.5 gm. Showed marked congestion.
XIII	9.5	4/4	.....	....	...	...	.....	....	....	....	.....	.....	....	.....	Right kidney removed, weighing 45 gm. Very tight band on left renal vein. All collaterals tied. Right renal vein thrombosed. Wt. 60 gm.
		5	Very sick	....	few c.c.	...	Full of blood	+	0.0	...	.....	.....	....	.....	
XIV	4.5	4/11	.....	....	...	...	Blood and casts	+	....	....	.....	.....	....	.....	Right kidney removed. Wt. 13.8 gm. Left kidney banded; access collaterals cut. Left kidney 28 gm. at autopsy. Veins thrombosed. Marked congestion.
		12	Very sick	1006	200	325	.....	....	1.5	8+	Intracardiac 24	Intracardiac 2.0	.75	.23	
		13	.....	....	...	...	.....	....	1.5	....	.....	.....	....	.....	
		14	Chloroformed	....	...	...	.....	....	....	...	.....	.....	....	.....	

From a study of this table it is at once evident that a kidney subjected to such usage does not suffer seriously over any great period of time. Even on the day following the operation the animal may appear normal. The urine is fair in amount, contains some albumin, red blood-cells, a few hyaline and granular casts, but the phthalein output in many instances is little, if any, reduced. The lactose, however, is invariably delayed markedly, the excretion of potassium iodid is usually considerably delayed and the salt not well excreted. As time progresses it becomes more apparent that the functional injury is slight—the phthalein output rapidly increasing to normal, if it has been at all reduced. Weeks or months after the operation the animal is normal to all appearances. A urinalysis, however, usually reveals a trace of albumin, in which microscopically a few granular and hyaline casts are seen. A functional study shows normal phthalein, iodid and salt excretion, while the lactose is slightly delayed.

The establishment of a good collateral circulation was thought to be probably responsible for the rapid return to normal of the kidney function.

The effect of ligating the vessels chiefly involved in collateral circulation of the kidney simultaneously with the operation described above was investigated. The band was placed about the renal vein at its entrance to the inferior vena cava. The ovarian vein, at its entrance to the renal, as well as one of its branches, a large vein which passes from the lower pole of the kidney to the ovary, was ligated. In some instances one of the lumbar veins and the suprarenal vein were also tied.

The results obtained from a study of this series of animals are shown in Table 2. These animals can be divided into two groups: Group I, including animals IX, X, XI and XV, in which the bands were of moderate tightness only, and Group II, in which the bands were made very tight. All four animals of Group I show a normal, or only slightly reduced, phthalein output at first. The quantity of urine excreted was large, contained albumin, but blood and casts were absent in two animals. The lactose was markedly delayed in all, salt excreted fairly well in two, and the iodid normally in two and delayed in another.

Dogs IX and X both showed a sudden marked drop in the phthalein output four or five days after the operation. The first subsequent examination of the urine showed large numbers of red blood-cells, probably indicating the occurrence of thrombosis in the renal vein, inasmuch as thrombosis was encountered at autopsy in each case. Dog X was particularly interesting, living for more than a week with a low phthalein output, the lactose, salt and iodid excretion being also very low. The urine was plentiful and of low specific gravity, contained much albumin, numerous red cells and a few casts. The dog throughout this period was

only in fair condition, at times playful and sprightly, but on the whole inclined to lie quietly and to sleep. Vomiting occurred at intervals.

Dog XV differed from the others of this group in that only one collateral channel was ligated, e. g., the ovarian vein just at its entrance to the renal vein. On the third day following operation the animal was only in fair condition. The urine was large in amount, containing considerable albumin and casts. The phthalein and iodid output were normal, while lactose was markedly delayed and salt excreted with great difficulty. At this time it became apparent that the dog was developing distemper. Later, on the seventh to the ninth days the albumin had disappeared and the only abnormal constituent present in the sediment was an occasional cast, the phthalein output being practically normal — 42 per cent. On the ninth day the animal died, the autopsy revealing a marked typical bronchopneumonia, no peritonitis, an immense left kidney with a tremendous amount of collateral circulation and beginning thrombosis, localized in the vein at the site of the band.

Group II is composed of two dogs, XIII and XIV. The bands placed on the renal veins of these dogs were very small. In Dog XIV the ovarian, and the veins at the lower pole which empty into the ovarian, lumbar and suprarenal veins were ligated. Both animals were exceedingly sick from the time of operation until death. Dog XIII excreted only a few cubic centimeters of urine after the operation. This was full of blood and no phthalein was recovered within an hour. The animal died after forty-eight hours. The kidney was found much enlarged, the band in place, with thrombosis of the vein. A tremendous subcapsular hemorrhage, the blood having partially dissected the capsule, was found. The kidney showed marked chronic passive congestion.

Dog XIV excreted 325 c.c. of urine on an intake of 200 c.c. of water on the day following operation. The urine contained albumin, blood and casts. The phthalein output was only 1.5 per cent., and the lactose markedly delayed. As the animal was vomiting repeatedly, the salt and iodid were administered by an intracardiac injection. The iodid was entirely excreted within twenty-four hours, but the salt was poorly excreted. Again on the following day only a trace of phthalein was recovered. The animal died on the fourth day. The kidney was double the normal size with the band in place. The vein was patent at the site of the band, but thrombosed distally. The capsular and ovarian veins were markedly engorged and a peculiar fleshy-like tissue* (probably hemorrhage) was found between the layers of the capsule in the region of the pelvis of the kidney. The animal also showed some bronchopneumonia.

To show the similarity of Cases XIII and XIV, from the point of view of urinary and pathological findings, to the picture following a

sudden complete ligature of the renal vein after removal of the opposite kidney, the data relating to Dog XII is included in this table. On the day following operation the animal was very ill and only a few cubic centimeters of bloody urine could be obtained on catheterization. This contained casts of various kinds—hyaline, granular and blood. After this no urine was obtained. At autopsy the kidney was found to weigh 52.5 gm. (R. 34 gm.) and to be dark violet in color. Between the layers of the capsule and in the tissues just outside of the capsule about the renal and ovarian veins was a large hemorrhage with clots of dark blood of varying age. The glomeruli were very distinct and markedly congested—more so than in any other kidneys met with in this study.

COLLATERAL CIRCULATION OF THE KIDNEY FOLLOWING GRADUAL BUT COMPLETE OCCLUSION OF THE RENAL VEIN AND THE CONDITION OF RENAL FUNCTION UNDER THESE CIRCUMSTANCES

It has been suggested in the earlier part of this paper that great importance is to be attached to the development of collateral circulation following gradual and progressive occlusion of the renal vein. An effort has been made to ascertain just how important collateral circulation may become in determining the state of renal function under such conditions.

Following the application of the band to the renal vein in dogs the capsular, ovarian, lumbar, suprarenal and ureteral veins become markedly engorged and distended. These enlarged vessels present a striking vascular picture which has been previously described by Litten.

The extent and tremendous importance of this development of collateral circulation is indicated by the following protocols:

Dog VIII.—Weight 6 kg.; had the right kidney removed and a moderately tight band placed about the left renal vein on January 27. Three months later the renal function had returned to normal save for a slight albuminuria and a slight delay in lactose excretion. A second operation was performed May 16, at which time it was seen that a tremendous collateral circulation involving the capsular, ovarian, lumbar, and suprarenal veins, had been established and that the renal vein itself was relatively small. The renal vein was tied and the abdomen closed. The animal's venous circulation, therefore, was entirely collateral. On the day following the operation urine was secreted which contained a large amount of albumin, blood and casts, but the phthalein excretion was 50 per cent. for an hour. During the next two days the animal was in good condition. The lactose was delayed over eight hours, but salt and iodid were excreted normally. At the present time, two weeks later, albuminuria and delayed lactose excretion still persist; otherwise the animal seems perfectly normal.

Dog IV.—Weight 10 kg.; had bands placed about both renal veins on Jan. 22, 1912. In the course of a few weeks function had returned practically to normal. On February 20 a second operation was performed, the left kidney being removed. The animal made a perfect recovery and the functions quickly again returned to practically normal. On May 24 a third operation was performed. The right kidney was found to be greatly enlarged and associated with a tremendous collateral circulation. The renal vein was tied at its entrance to the vena cava, the

abdomen closed and the animal allowed to recover. On the following day the dog was in good condition with a fair urinary secretion (250 c.c.) containing albumin, blood and casts. The phthalein output was 40 per cent. Two days later the lactose was found to be delayed for more than eight hours. Salt and iodid were excreted normally. The animal was in excellent condition, but the wound was badly infected.

In two instances this remarkable condition has been seen, e. g., an animal living in apparently good health, secreting practically a normal urine and exhibiting an excellent condition of renal function with the renal vein tightly ligated. This affords striking evidence of the great importance of collateral circulation where gradual obstruction to the venous return from the kidney develops.

Although, owing to different anatomical conditions in humans, so great a development of collateral circulation may not be possible, it undoubtedly is a matter of extreme importance where gradual venous obstruction occurs.

To summarize, then, it is evident that, after a one-sided nephrectomy, the application of a moderately tight band about the other renal vein causes marked congestion of the remaining kidney. The congestion is associated at first with the production of a good quantity of urine which contains usually albumin and casts and sometimes blood. The excretory capacity of the kidney is not seriously injured, as evidenced by a good phthalein output. The excretion of lactose is always markedly delayed, as is usually also that of the iodid and salt. With the development of a good collateral circulation the congestion becomes less intense, the albumin, blood and casts become a less pronounced feature of the urinary picture. The phthalein, iodid and salt may all be normally excreted, but the lactose is still delayed. Two or three months after such an operation the most probable abnormalities will be a very slight trace of albumin and a delayed lactose excretion.

When a moderately tight band is applied and the collateral channels ligated, the same picture is encountered during the following two or three days as is seen when the collaterals are left open. Thrombosis of the renal vein is apt to develop, however, and its occurrence is associated with the appearance of a large amount of blood in the urine and a sudden marked fall in the phthalein excretion. Nausea and vomiting develop. The amount of urine at first may be large. All the excretory functions finally fail and death ensues.

When an excessively tight band is applied to the renal vein and the collateral channels are ligated, the effect is usually similar to that which would be encountered following complete ligature; e. g., large amounts of albumin and blood, together with the excretion of minimal traces of phthalein, lactose, iodid and salt. Thrombosis occurs and death results.

The magnitude and importance of the development of collateral circulation following gradual obstruction to the return venous flow is indicated by the demonstration of the possibility of animals living and exhibiting a good renal function where the occlusion of the renal vein has been gradual, but complete.

THE EFFECT OF PLACING A BAND ABOUT ONE RENAL VEIN; THE OTHER KIDNEY REMAINING UNDISTURBED. URETERAL CATHETERIZATION OF BITCHES

Experiments were also made for the purpose of determining the effect on the urinary picture and on the total renal function of applying a band to one renal vein, the other kidney being undisturbed. Simultaneously, a comparative study was made of the urine from a normal kidney and that from a kidney with chronic, passive congestion in the same animal. By such a method it is possible to determine the effect *per se* of congestion on function.

In order to determine the function of each individual kidney it was, of course, necessary to collect the urine separately from the two sides. This was done by means of ureteral catheterization and was accomplished without discomfort to the dog. The animal was tied down on its back with comfortable holding straps and the ureteral catheters introduced in the manner constantly employed in the clinic.

In order to use the ordinary instruments for ureteral catheterization, large bitches are necessary. It would be possible to use comparatively small bitches if a single-barrelled catheterizing instrument large enough to carry a single No. 6 F. catheter were employed. In order, however, to catheterize both ureters, and at the same time carry catheters large enough to obturate them effectively, an instrument of at least 24 F. must be employed. The ureteral orifices are readily recognized in the bitch, and as a rule but little difficulty is encountered in entering them. But, owing to the curved course of the ureter in the vesical portion, passing the catheter higher than 2 cm. frequently requires considerable manipulation.

The Brown-Buerger catheterizing cystoscope No. 24 F. and No. 6 flute-end catheters were used in all of our experiments. When the internal orifices cannot be recognized readily, an injection of indigo carmin intramuscularly will, within a few minutes, clearly indicate their positions.

BITCH XVI.—Weight 18 kg.; showed a normal renal function as determined by functional tests. On January 18, a moderately tight band was applied about the left renal vein. Five days later the phthalein output was practically normal.

On February 9, both ureters were catheterized without anesthesia by the technic described above. The urine was obtained for twenty minute periods as follows:

TABLE 3.—URINE FROM BITCH XVI WITH BAND ON LEFT RENAL VEIN

FIRST PERIOD

Amount, c.c.		Sulphonephthalein, Per Cent.		Indigo Carmin, Per Cent.		Sp. Gr.		Urea, Gm.	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
1.9	*1.0	63.3	100	59.0	100	1.010	1.030	0.0145	0.015

SECOND PERIOD

2.1	1.3	64.7	100	64.1	100	1.005	1.014	0.015	0.021

*The urine from the side having the smaller amount was diluted to the quantity of the other and then the two urines compared in the Duboscq colorimeter. The diluted urine of the right side was much more intensely colored than that of the left. In these tables the relative amount of dye substance of the side containing the smaller amount is expressed as percentage of the other.

TABLE 4.—URINARY FINDINGS IN BITCH XVI AFTER 300 C.C. WATER BY STOMACH TUBE

FIRST PERIOD

Urine c.c.		Sp. Gr.		Sulphonephthalein, Per Cent.		Indigo Carmin, Per Cent.		Sodium Chlorid, Per Cent.	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
6.7	5.0	1.010	1.017	79.0	100	78	100	....	....

SECOND PERIOD

6.0	7.0	1.010	1.019	73.2	100	67	100	0.20	0.36

THIRD PERIOD

4.3	6.9	1.010	1.010	....	...	..	...	....	....

February 16, 300 c.c. of water was given by stomach tube one-half hour before catheters were in place. The right ureter was catheterized and the urine of the left side collected transvesically. The leakage was practically zero—not more than 0.5 c.c. for any period of twenty minutes.

On March 19, a phthalein test was made in the usual way, showing an output of 70 per cent. in one hour.

On April 3, the animal was killed by bleeding, owing to severe septic infection from a wound in the leg. The kidneys were found to be of about equal weight, 48 gm. each. The band was in place, exerting but moderate pressure on the vein, which was patent and free from thrombosis. The cut surface of the kidney did not exhibit marked evidence of congestion. There was thinning of the cortex in two or three areas at the lower pole, over which areas the capsule was found to be adherent. The capsular veins of the left kidney were markedly engorged and there was considerable enlargement of the vessels concerned in the collateral circulation.

Bitch XXII.—Weight 8 kg.; was subjected to operation on May 10 and a moderately tight band placed about the left renal vein. Ten days later the animal was in excellent condition, the phthalein output normal. Chlorbutanol was administered by stomach tube, the lower abdominal wall opened in the median line and the bladder exposed. The urethra was tied and the bladder sewed down the middle from the urethra to the apex of the bladder, with a fine needle and fine silk. A glass bladder-cannula was then placed in each half of the bladder. In order to start urinary secretion it was found necessary to inject 40 c.c. of 5 per cent. NaCl solution intravenously. The urine was then collected from each side separately for one hour periods. The results of these studies are tabulated below:

Table 5.—Urinary Findings in Bitch XXII With Band Around Left Renal Vein

FIRST PERIOD

Urine, c.c.		Sp. Gr.		Sulphonephthalein, Per Cent.		Urea, Mg. Per c.c.		Indigo Carmin, Per Cent.		Lactose, Gm.		Carbolfuchsin, Per Cent.	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
16.7	14.0	1.013	1.009	83	100	4	10	..	...	..	..	..	...

Total phthalein output 46 per cent. for one hour.

SECOND PERIOD

16.4	15.0	1.034	1.035	..	...	10	15	..	...	1-1	1-1	..	...

THIRD PERIOD

10.5	12.4	1.031	1.028	..	...	..	..	93	100	..	..	..	...

FOURTH PERIOD

10.8	11.2	1.015	1.007	..	...	..	..	..	...	..	..	60	100

Total N. from 10 c.c. of mixed urine from left side, 0.0536 gm.
Total N. from 10 c.c. of mixed urine from right side, 0.0658 gm.

On opening the abdomen the left kidney appeared considerably larger than the right and a good collateral circulation had developed. In order to demonstrate that there was no communication between the two halves of the bladder, water was slowly injected into one half, and recovered through the corresponding catheter, without any flow from the other side. The animal was killed by bleeding. The right kidney weighed 25 gm. and the left 25.5 gm.

These experiments are interesting and instructive from several points of view. A greater excretion of urine has been encountered on the side where the venous return was obstructed in several observations which, in one case, extended over a period of weeks. *This bears out the contention of Schwarz as to the possibility of encountering increased urinary output with obstruction to venous return, and directly disproves the claims of Paneth and de Souza.* It shows, further, that even in the presence of the relative polyuria on the congested side that the per cent. of solids, as indicated by the phthalein, indigo-carmin, lactose, urea and salt content, is greater from the normal than from the congested side. The experiments further suggest that the water goes by preference through the slightly congested kidney, whereas the excretion of solids is considerably interfered with. The uniform relative excretion of the same dye on different occasions, as well as the parallelism of the excretion of different dyes at the same observation, is exceedingly striking. The truth of Albarran's claim, i. e., that with forced fluid the extra demand for secretion is responded to by the normal kidney, is demonstrated by the greater output of water from the right kidney in the second and third period of the first experiment. The excess from the right kidney began at the proper period at which the polyuria should appear. The fact that the water only, and not the salt, lactose, carbol-fuchsin, the indigo-carmin and phthalein, are increased is also significant.

BANDS ON THE AORTA BELOW LEVEL OF RENAL ARTERIES

A greater quantity of blood was directed through the kidney by cutting off to a considerable degree its escape from the aorta below. Moderately tight bands, which constricted the aorta to approximately half its normal diameter, were applied just above its bifurcation. This experiment alone was performed on one animal, combined with a nephrectomy on a second, and with nephrectomy and a band on the renal vein on the third. The following protocols indicate the results:

Bitch XVI.—Weight 5.5 kg., operated on February 12. A fairly tight band was placed on the aorta below the renal arteries so that the vessel was decidedly larger above and smaller but still pulsated below the band.

February 13-16. Dog in excellent condition. Normal quantity of urine containing a few hyaline and granular casts. Phthalein and salt excreted normally; iodid delayed to seventy hours. Lactose delayed to seven hours.

February 27-28. Phthalein, salt, iodid and lactose all excreted normally. Animal in good condition. Here we have an entirely normal renal function.

March 4. Animal developed distemper and died.

Autopsy: Bronchopneumonia. No peritonitis. The aortic band is in place buried in fibrous tissue. The aorta is patent, standing out well above band, but is much smaller below. The kidneys are probably slightly enlarged, and combined weight 50 gm.; are dark blue in color.

Hyperemia, therefore, caused the appearance of casts in the urine, together with a delayed lactose and iodid output, which rapidly returned to normal.

Bitch IX.—Weight 7 kg.; had a right-sided nephrectomy and a tight band about the aorta just above its bifurcation, on February 17. On the following three days the animal was in poor condition, showing evidences of peritonitis. The urine output was rather small in amount, the phthalein and iodid normal, lactose delayed and salt poorly excreted. On the 23rd the animal was chloroformed. The autopsy revealed peritonitis and retroperitoneal abscesses. The band was found in place, the aorta enlarged above it. The kidney was dark, purplish-red in color, deeply engorged and weighed 45 gm. The capsule strips readily.

Dog XVIII.—Weight 9 kg.; March 4 had a right-sided nephrectomy performed, the kidney weighing 38.5 gm. A band was placed on the aorta just above its bifurcation, causing marked constriction, and a second band of moderate size was placed about the renal vein at its entrance into the vena cava.

March 5. Animal in good condition exhibiting a polyuria—1,000 c.c. output on 700 c.c. water intake. Urine contains a trace of albumin and a few hyaline casts, but no blood cells. The phthalein output is reduced to 29 per cent. Lactose delayed to seven hours; iodid normal. The salt is excreted poorly in low concentration, .09 per cent., yielding a total of .9 gm. on a 3 gm. intake.

March 6. Polyuria persists—900 c.c. urine on 700 c.c. water intake. Salt concentration low—0.11 per cent.

March 7. Phthalein output normal, 50 per cent. Polyuria 750 c.c. on 700 c.c. intake. Salt concentration is low—0.12 per cent.

March 8. Phthalein normal, lactose delayed—eight hours; iodid seventy-two hours. The fluid excretion was not noted.

March 11. Phthalein normal, 60 per cent. Animal shows signs of distemper developing. Urine contains a trace of albumin, but no casts or blood.

March 13. Animal died with symptoms of distemper. At autopsy the kidney was found intensely congested. Weight 60 gm. Both bands were in place and both vessels patent. An abscess containing about 5 c.c. of pus was found in the region of the aortic band. Some fibrinous peritonitis was also found.

This experiment is of peculiar interest on account of the occurrence of a definite persisting polyuria associated with venous obstruction, which coexists with an excessive amount of blood flowing into the kidney.

CONTROLS

It was considered desirable to see what effect on the renal function was produced by simple unilateral nephrectomy. The first dog, in addition to a right-sided nephrectomy, had the left renal vein isolated from the surrounding tissue just as is done in each of the experiments when the band is applied.

Dog XX.—Weight 6.9 kg.; nephrectomy performed on February 26.

February 27. Phthalein 57 per cent. Iodid eighty hours. Lactose eight hours +. Sodium chlorid excreted in good concentration.

March 18 and 19. Urine normal in quantity. No albumin or blood, an occasional hyaline cast. The phthalein output was normal, as was also the salt. The lactose was very slightly delayed—6½ hours; but the iodid was not excreted in less than seventy-two hours.

April 14. The phthalein, salt, iodid and lactose were absolutely normally excreted, and the urine itself was entirely normal.

Dog XXI.—Weight 5 kg., April 24. Right kidney removed; weight 17.8 gm.

April 25. Phthalein 38 per cent.; slightest trace of albumin, an occasional cast seen in centrifugalized specimen.

April 27. Phthalein normal—55 per cent. Lactose delayed seven hours, salt excretion somewhat delayed.

May 3 to 9. The salt, lactose and phthalein excretions are all normal, the only abnormal urinary feature being a very faint trace of albumin.

Simple one-sided nephrectomy in a healthy dog, therefore, causes but slight change in the renal function which is of short duration.

INCOAGULABLE NITROGEN OF THE BLOOD IN CHRONIC PASSIVE CONGESTION

In five cases of animals with a moderate degree of chronic passive congestion, and with relatively normal renal function, and in one with marked congestion, the incoagulable nitrogen of the blood was estimated. The technic employed was as follows: 10 c.c. of blood was withdrawn from the heart and placed in 115 c.c. of 95 per cent. alcohol to precipitate the albumin. This was filtered, and 100 c.c. of the filtrate evaporated to dryness. The total nitrogen of this residue, representing 8 c.c. of blood, was estimated by Kjeldahl's method. In the five nearly normal cases, the nitrogen was not increased above 0.50 gm. per liter of blood. In the dog with advanced congestion, the nitrogen was increased to 0.60 gm. per liter.

It can be concluded, therefore, that mild experimental chronic passive congestion in dogs does not produce an accumulation of incoagulable nitrogen in the blood.

HISTOLOGICAL STUDY

The histological study[52] of the kidneys removed at autopsy was made as follows: The kidneys were fixed in formaldehyd solution or Zenker's fluid, cut and stained with hematoxylin and eosin. The microscopic study in all cases revealed varying degrees of chronic passive congestion of all the vessels and capillaries. In certain of the cases there were foci of leukocytes or small abscesses. In one case there was considerable increase in connective tissue suggesting a chronic nephritis. Whether this was due or not to the congestion cannot be stated. On the whole, histologically, it seems that by this method, chronic passive congestion of varying intensity is produced without an accompanying chronic nephritis.

52. A further study of the histological changes following more prolonged chronic passive congestion is intended.

CONCLUSIONS

1. By the technic described it is possible to produce over short periods any grade of chronic passive congestion desired.

2. Slight experimental chronic passive congestion of the kidney is characterized by (a) a normal quantity of urine which contains a trace of albumin, intermittently a few hyaline and granular casts and occasionally a few red blood-cells; (b) the functional capacity varies but little from normal, since phthalein, salt and potassium iodid may be all normally excreted, while lactose excretion is but slightly delayed.

3. Moderate experimental passive congestion of the kidneys is characterized by (a) a fair amount of urine containing albumin, casts and frequently red blood-cells; (b) a total excretory capacity which is apparently not markedly decreased, since the phthalein excretion is usually normal. The excretion of salt is usually somewhat decreased, that of potassium iodid variable, that of lactose invariably delayed.

4. Marked experimental chronic passive congestion of the kidneys is characterized by (a) very scanty amounts of urine containing a large amount of albumin, casts and red blood-cells; (b) a much reduced functional capacity, since the phthalein, salt and lactose excretions are markedly delayed, as is also frequently that of iodid.

5. Albuminuria is almost a constant accompaniment of experimental passive congestion, casts are usually present, and red blood-cells appear if the congestion is of any considerable degree.

6. Lactose excretion is the first to become affected by increasing grades of chronic passive congestion; then the excretion of salt and iodid, and lastly, that of phthalein.

7. The phthalein test gives the most reliable information concerning the degree of renal insufficiency in experimental chronic passive congestion. Marked delay in the excretion of lactose, iodid and salt has, indeed, been encountered in animals showing a normal phthalein output. These animals were, however, apparently in good general condition, while subsequent events showed that they remained in good condition. On the other hand, a marked decrease in phthalein excretion has invariably been associated with the development of clinical manifestations, indicating renal inadequacy and followed by death. The phthalein test is, therefore, the test of greatest prognostic importance in chronic passive congestion.

8. Lactose, while of least value in revealing the degree of involvement of renal function in experimental chronic passive congestion of the kidney, is of the greatest value in detecting its existence. It is, therefore, of these tests that of greatest diagnostic, but of least prognostic value.

9. The excretion of potassium iodid is usually prolonged in experimental chronic passive congestion of the kidney. The time of elimination of this drug is, however, so variable that the test proves practically valueless in this connection.

10. The excretion of sodium chlorid is usually decreased where moderate or marked experimental passive congestion is present.

11. Partial obstruction to venous return through the renal vein is not invariably associated with decreased urinary secretion. In an apparently normal unanesthetized or anesthetized (chlorbutanol) animal which has partial occlusion of one renal vein only, more urine is sometimes excreted from the congested kidney, while the solids are excreted in greater concentration from the normal side.

12. Where gradual progressive obstruction to the renal vein occurs, the development of a collateral circulation is of great importance in maintaining the functional capacity of the kidney since an efficient renal function may be encountered when the venous return from the kidney is entirely collateral. On the other hand, ligation of collateral vessels, simultaneously with a moderate degree of obstruction to the renal vein, usually results in renal inefficiency and death.

13. An excessive flow of blood through the kidney simultaneously with an obstruction to its outflow may be followed by polyuria.

14. Mild grades of experimental chronic passive congestion are not associated with the accumulation of incoagulable nitrogen in the blood.

15. Varying degrees of chronic passive congestion which are unassociated with nephritis are produced by the above-described procedures.

AN EXPERIMENTAL STUDY OF POISON OAK*

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While it is true that poison oak and its sister plants have rarely, if ever, caused a death, it is also true that a large majority of people living in the temperate zones find their enjoyment of the country seriously curtailed by the menace of these noxious plants. And besides this restriction of healthful pleasures, there is an unestimated monetary loss to laborers and construction companies operating in infested regions, which I am sure is not inconsiderable. Yet in spite of these well-known facts, very little has been attempted, and still less accomplished, to abate this wide-spread evil.

SKETCH OF PLANT

The plants specially referred to are poison oak (*Rhus diversiloba*), poison ivy (*R. toxicodendron*) and poison sumach (*R. venenata*), which form a widely distributed group. The poison ivy[1] is found in abundance throughout the United States as far west as eastern Texas, eastern Kansas and Minnesota, and in greater or less abundance throughout the less arid regions of the west, with the exception of California and the western parts of Oregon and Washington, where it appears to be entirely replaced by the poison oak. The plants are very similar to each other, each being a shrub that trails along the ground, or climbs fences, trees or brush, or in many instances stands erect independently. It does not frequent the higher mountains. The irregularly lobulated and dentated leaves of the poison oak are a beautiful red when young, and an equally attractive russet when old, rendering them enticing to the uninitiated. The fine hairs that are found on the leaves, especially along the margins, are supposed by some to carry the poison when wafted by breezes, thus explaining poisoning at a distance. The berries and blossoms are green and extremely poisonous. But the berries turn white as they ripen, lose their poison and are often eaten by birds, which are the means of distributing the plants over so wide a territory.

THE TOXIC PRINCIPLE NON-VOLATILE

While poison oak, poison ivy and poison sumach differ botanically, their juices seem to be chemically identical. Franz Pfaff,[2] of the Harvard

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1. Chestnut: Farmer's Bulletin No. 86, U. S. Dept. Agriculture.

2. Pfaff: Jour. Experimental Medicine, 1897, (2), 181.

Medical School, in his excellent monograph, states that the poison is identical in the ivy and in the oak. That the dermatitis caused by either plant is identical clinically, has been recognized for a long time. Several attempts have been made to isolate chemically the poisonous principle of the plants. This problem is of special importance because it underlies much of the clinical and biologic work.

The earliest attack on this difficult problem was made in 1779 by van Mons,[3] who concluded that the poison was a "gaseous hydrocarbon," emanating from the plant only at night or on cloudy days. Lavini, writing thirty-three years later (1825), also believed the poison to be a gas exhaled at night, but thought it was not a hydrocarbon. Another thirty-three years then elapsed before Khittell (1858) analyzed the plant and derived his "rhustannic acid." But he said that there was also a volatile, toxic alkaloid. In 1865, Maisch isolated his "toxicodendric acid," again a volatile substance. Then followed two Japanese, Ishimatsu and Yoshida (1882 and 1883), who also concurred that the toxic agent is volatile. The chemical problem really had but little light thrown on it until Pfaff approached the problem from the clinical viewpoint and showed that Maisch's "toxicodendric acid" is entirely inert; indeed, nothing but acetic acid, and that contrary to all previous impressions, the toxin is actually a non-volatile substance which he extracted and named "toxicodendrol" on account of its oily appearance. Of this substance, as little as 1/1,000 mg. suffices to produce the typical dermatitis.[2] All parts of the plant yield toxicodendrol, the leaves and green berries, however, more in proportion to weight. The best and most recent chemical study of the toxin is than of W. A. Syme,[4] whose dissertation on "Some Constituents of the Poison Ivy," was accepted by Johns Hopkins University in granting him the degree of Ph.D. in 1906. His analysis shows that the poison is a complex substance of a glucosidal nature, yielding, on analysis, gallic acid, fisetin and rhamnose. The poison was again shown to be non-volatile, even when mixed with acetic acid (with which it is naturally associated in the plant), or with alcohol.

Thus it is seen that for a hundred and eighteen years, from van Mons to Pfaff, the opinion prevailed that the toxin was volatile — a natural conclusion in the presence of the common observation that persons are poisoned while simply passing near the plant, without actual contact. The importance of Pfaff's work, confirmed and enlarged by Syme, is therefore evident. Before dismissing the subject of the nature of the poison, it may be noted that a bacterial theory had its supporters, but its proponent (Burrill, 1882) admitted (1895) that proof was lacking. That

3. L. E. Warren has compiled an extensive and excellent bibliography in The Midland Druggist and Pharmaceutical Review, 1910, xliv, Nos. 3, 4 and 5.

4. W. A. Syme: Johns Hopkins Univ. Bulletin, 1906, "Some Constituents of the Poison Ivy Plant."

the poison is not bacterial is to-day very clear, although bacteria often play an important rôle as agents in secondary infection.

POISONING WITHOUT CONTACT

The toxic principle having been shown to be non-volatile, the practical question immediately presents itself, how does poisoning at a distance occur? That persons are poisoned without direct contact with the plant is too common an observation to be denied. The explanation is doubtless the mechanical transportation of the poison, as happens when the pollen, or the plant hairs, or other dust from the plant is carried by air-currents. Or, perhaps as commonly, the transporting agents are simply clothes, or tools or animals, which, after brushing against the plant, are able to transfer the poison to susceptible persons. Such explanations are easily acceptable when one remembers how minute a quantity suffices to induce inflammation. In order to show that the poison is not volatile the following experiment was made:

Experiment 1.—Young, fresh poison oak leaves were crowded into a glass tube, one end of which was closed with cotton. Holding this end against the skin of a susceptible person, air was blown through the tube. The spot struck by the air current was then covered with zinc oxid plaster to retain what poison might have been deposited, and after forty-eight hours the spot was inspected. Were the poison volatile, dermatitis should have resulted. The result was negative.

On the other hand, I was severely poisoned by the dust raised while handling the dried plants in the laboratory.

SMOKE FROM BURNING PLANTS IS POISONOUS

Another fact of interest, amply sustained by popular personal testimony, is that the smoke of burning rhus plants is especially toxic. This is somewhat surprising after reading Pfaff's statement[2] that "toxicodendrol is decomposed easily by heat." The degree of heat required is not mentioned. On this point the following experiment was made:

Experiment 2.—Fresh green leaves were placed in a test-tube closed with cotton, and submerged (except the open end) in boiling water for one hour. Dermatitis was readily secured by contact with the boiled leaves, thus showing that the poison is not destroyed by 100 C. for one hour.

The literature presents no evidence on this point. The above experiment supports the popular belief that smoke from burning rhus (especially if the plant is green) carries the poisonous juice of the plant. It is probable that in a heated state the juice more readily penetrates the epidermis and causes toxic inflammation.

Experiment 3.—In order to make this test more positive, *dried* rhus leaves were crowded into a glass tube, to one end of which was attached a rubber mouth piece. The glass was then held in the flame until the leaves burned. While blowing gently through the tube, the smoky current was caused to impinge on the skin

of a susceptible person. The spot was then covered with zinc oxid plaster to retain what poison may have been deposited. Characteristic dermatitis developed in twenty-four hours.

THE OCCURRENCE OF THE ERUPTION

Because the spots of dermatitis often break out successively in widely separated areas of the skin, the impression has gained credence that the poison is distributed by the blood-stream—a matter of considerable importance in its bearing on the pathology and treatment of the disorder. Light was thrown on this question by Pearson (1880), who showed experimentally that serum from the vesicles is not toxic. I have repeatedly tried in vain to produce dermatitis by rubbing in the serum from vesicles. Chestnut[1] also concludes that the dermatitis is purely local, and is never distributed by the blood. The following experiment is deemed conclusive on this point:

Experiment 4.—I frequently poisoned limited skin areas and prevented any spread of the toxin by covering it immediately with zinc-oxid plaster. Under these conditions a dermatitis never occurs in any other than the exact spot where the toxin is applied.

It is easily conceived, however, that in natural exposures several elements would tend towards the occurrence of dermatitis in crops rather than at all points simultaneously. Before all the poison has penetrated, some of it might easily be transferred to other areas, thus producing a new crop. Again, the poison might be transferred to new areas from clothes or hair. Furthermore, it is not unlikely that where the skin is thin, as on the face, wrists, etc., the time necessary for penetration—the latent period—is shorter than where the skin is thicker—again accounting for succession rather than for simultaneity.

PHYSIOLOGICAL PATHOLOGY

The exact physiological nature of the poisoning by rhus juice has never been studied. This is not surprising when one realizes that the exact nature of the toxin is still not fully known. The chemical problems must first be solved before the physiologist can offer any explanation of why this peculiar glucoside should cause inflammation. That there are variations in general or local susceptibility in different individuals and in the same individual at different times, cannot be doubted. But the exact property of cells or fluids of the body that determines susceptibility to rhus is as yet a mystery.

RELATION TO SWEAT REACTION

Misled by Maisch's statement that the poison was an acid, I made a series of observations some years ago on sweat reactions as determined by litmus paper, to see whether acidity or alkalinity of the sweat bears any relation to susceptibility to the poison.

Experiment 5.—A number of sweat reactions were taken and recorded, each person being asked whether he was susceptible to the poison. Of each class—acid, alkaline, and neutral—there were some susceptible and some immune. Among them was one person with strongly acid sweat who was extremely susceptible. But there was another equally susceptible whose reaction was strongly alkaline. So that no relation to sweat reaction could be determined even though account was taken of the physiological change of reaction during exercise.

VACCINATION AND IMMUNITY

Considerable popular testimony is available upholding the possibility of vaccination against rhus by ingestion of the plant or its derivatives. There are those who state that the tincture of the fluid extract taken internally prevents attacks on subsequent contact with the plant. Likewise, many persons claim to have gained immunity by chewing or eating small quantities of the rhus leaves. This prophylactic measure is said to have been found valuable by the engineers of the Union Pacific Railroad Company while the line was being built through poison oak country. Similar testimony is obtained from residents in the Adirondack Mountains. And I am told by an eye witness that Indians and other residents of New Mexico habitually eat the leaves each spring to avoid poisoning during the summer. Experimental confirmation or scientific observation of these folk-sayings is, however, entirely lacking. But they open the large question of acquired immunity. Ford[5] states that there is no difficulty in showing that many persons are quite resistant to the action of rhus toxin. On the other hand, the same writer expresses the opinion that the so-called natural immunity is really an acquired immunity. He raises the question, obviously difficult to answer, whether "the cases of supposed natural immunity do not occur in individuals in whom as children the effects from handling the plant have gradually worn off, the original dermatitis having been so insignificant as to have escaped notice, or being so many years distant as to have been forgotten." He concludes that complete natural immunity, when put to experimental test, is exceedingly rare. Warren[6] likewise thinks that "the belief in absolute immunity is a delusion." Desiring to settle this question by experimental evidence I made the following tests:

EXPERIMENTS ON IMMUNES

Experiment 6.—A. B. claims he acquired immunity through several severe attacks. A fresh rhus leaf was applied to each forearm and held in place by plaster. Both applications caused marked dermatitis.

Experiment 7.—E. L. claims natural immunity from birth. A fresh rhus leaf was applied to each arm and held in place by plaster. Slight dermatitis was caused on each arm.

5. W. W. Ford: "Antibodies to Glucosides with Special Reference to Rhus Toxicodendron," Journal Infectious Diseases, 1907, iv, No. 4.

6. L. E. Warren: "The Poisonous Principle of Rhus," Pharmaceutical Jour., Oct. 30, Nov. 6, 1909.

Experiment 8.—D. S. claims acquired immunity except from the smoke. A fresh leaf was applied to each arm and held in place by plaster. Both spots showed dermatitis.

Experiment 9.—J. C. claims natural immunity from birth. She therefore offered to gather rhus leaves for me. While bringing them in she held them as one does a bouquet, against her chest. The waist being cut low permitted the leaves to touch the skin. Numerous mild spots of dermatitis developed.

Experiment 10.—E. F. claims immunity from birth. She accompanied J. C. gathering leaves. But she developed no dermatitis. Believing her immune, she was engaged to gather a larger quantity of leaves. After this exposure of about three hours among the February leaves, she developed numerous troublesome spots.

Experiment 11.—L. A. claims immunity from birth. Tested with tincture of rhus on forearms, he developed red itching spots.

Experiment 12.—A. R. claims immunity from birth. He never has been poisoned, though exposed.

Test 1: Rubbed fresh green leaves on forearm. Result negative, though observed for one week.

Test 2: Put active tincture on arm. Result negative after several days.

Test 3: Applied alcohol solution of pure toxin to the wrist. Result negative after three days.

Test 4: Applied same to forearm and covered with plaster. Result negative after three days.

Test 5: Applied active tincture rhus to forearm, covered with zinc oxid plaster. Result negative after several days.

Test 6: Believing him immune, he was sent to gather a sack of leaves. Eleven days later he noticed spots of dermatitis with itching and his face became swollen. Rhus dermatitis was markedly developed on face and arms.

Thus of seven "immunes" tested, all responded to the poison. *This indicates universal susceptibility to this toxin.*

ANIMAL IMMUNITY

Whether immunity can be induced experimentally in animals is an important problem that was attacked by W. W. Ford[5] (1907). His experiments were done on rabbits and guinea-pigs, using fresh fluid extract of *Rhus toxicodendron*. He states that after subcutaneous injection of a toxic dose, there elapses a latent period of seven or eight days in which the animal loses weight and dies at the end of another week of nephritis. Incidentally, a slough is formed at the site of injection. The estimated toxic dose for a 250 gm. guinea-pig was 0.25 c.c., and for an 800 gm. rabbit, 1 c.c. On the basis of these toxic doses, he gave repeated small doses at intervals of a few days, and claims to have immunized animals so that they resisted successfully five or six times their fatal dose.

Such immunized animals showed no nephritis when killed. The serum from these immunized animals protected other animals completely against fatal doses of fluid extract of rhus. Thus Ford appears to have produced active and passive immunity in these animals. These results, however, are inconclusive because of the unfortunately small number of experiments, and because of the material used—the fluid alcoholic extract, which contains, besides an indefinite amount of rhus toxin, various unde-

termined extractives of the plant, some glycerin, and as much as 58 per cent. of alcohol. Furthermore, in a personal communication Ford states that he was unable to get the same results a second time, attributing the failure to impotency of the fluid extract.

COMMERCIAL FLUID EXTRACT OF RHUS

An attempt was made to repeat Ford's work on animals, but the doses he found to be toxic were without effect. The material used was Wyeth's fluid extract of *Rhus radicans*.[7] The result is seen in Table 1.

TABLE 1.—SUBCUTANEOUS INJECTIONS OF GUINEA-PIGS WITH WYETH'S FLUID EXTRACT OF RHUS RADICANS, CONTAINING 58 PER CENT ALCOHOL

No. Pig	Weight, Gms.	Wyeth's Fld. Ext. c.c.	Time Observed, Days	Result
1	585	5	5	In 24 hours sick; dead 5 days.
5	240	3	1/6	Drunk 5 minutes; dead 1 day.
9	440	1	16	Negative; gained weight steadily; no induration

Although the larger doses kill guinea-pigs, controls with the corresponding amount of alcohol alone, died, and exhibited the same induration and necrosis at the injection site as described by Ford (see Guinea-pigs 10, 18, 20 and 19, Table 2).

TABLE 2.—GUINEA-PIGS RECEIVING SUBCUTANEOUS INJECTIONS OF ALCOHOL

No. Pig	Weight, Gms.	Alcohol, c.c.	Per Cent.	Water, c.c.	Time Observed, Days	Result
8	280	1.0	95	...	19	Induration and necrosis.
6	210	3.0	95	...	..	Drunk; dead in few minutes.
4	335	3.0	95	...	..	Drunk; dead in few minutes.
10	440	1.5	95	...	17	Stupid; large necrosis; died.
18	410	1.0	60	...	2	Site softened, wt.=420 gm.
18	420	2.0	60	...	10	Large necrosis; wt.=250 gm.; died; no nephritis.
20	310	2.0	60	2.0	9	Drunk; necrosis; wt.=250 gm.; died; infected; no nephritis.
19	360	2.0	98	1.0	11	Drunk; necrosis; wt.=220 gm.; died; infected; no nephritis.

Tables 3 and 4 seem to indicate that the alcohol solution of rhus toxin is somewhat more toxic than the same amount of alcohol alone. However, the short time intervening between the injection and death argues in favor of the alcohol alone being responsible for the death. This is referred to later.

7. *Rhus toxicodendron.*

TABLE 3.—RESULTS OF INTRAVENOUS INJECTIONS OF 95 PER CENT. ALCOHOL IN RABBITS

Rabbit No.	Weight, Gms.	Alcohol, 95 Per Cent.	Time Observed Days	Result .....
10	2140	0.5	4	Negative
6	1050	1.0	7	Negative
10	2040	1.0	2	Negative
4	2560	1.0	1	Negative
5	1500	1.0	1	Negative
7	780	2.0	¼	Died

TABLE 4.—RESULTS OF INTRAVENOUS INJECTIONS OF ALCOHOLIC SOLUTION OF RHUS TOXIN IN RABBITS

Rabbit No.	Weight, Gms.	Toxin, Gms.	Alcohol, 98 Per Cent., c.c.	Time Observed Days	Result .....
6	1015	0.0125	0.5	5	Negative
6	1160	0.0125	0.5	7*	Negative
10	2240	0.0125	0.5	7	Negative
4	2550	0.0125	0.5	7	Negative
4	2560	0.01625	0.65	..	Died immediately
9	2045	0.025	1.0	..	Died immediately
11	2580	0.025	0.5	46	Negative
8	1900	0.05	2.0	..	Died immediately

*Additional.

Not desiring to work further with a substance containing an unknown quantity of the poison, besides alcohol, glycerin and other undetermined substances in considerable quantities, the plant was collected and the pure toxin extracted after the method recommended by Syme: Fresh leaves of poison oak are thoroughly extracted with absolute alcohol. After filtration, lead acetate in water is added till precipitation is complete. The precipitate is then washed well and dried at a low temperature, when it is extracted in Soxhlet extractors for at least ten hours. The ether extract is then mixed up with water and treated with hydrogen sulphid, to separate the lead. The water and ether are then separated, the ether filtered, and well washed, after which it is evaporated at a low temperature. The presence of the toxin is then confirmed by testing for glucoside (Molisch's test) and by application to the skin, the physiological test. This toxin was carefully weighed and dissolved in absolute alcohol, so that 1 c.c. contained 0.0125 of pure toxin.

INTRAVENOUS ADMINISTRATION OF SUSPENSION

Noting that alcoholic menstruums, such as the fluid extract, produce marked induration at the site of subcutaneous injection, thus rendering problematic the amount of toxin entering the general system, it was determined to introduce the toxin intravenously. But both alcohol and ether when employed in workable quantities, intravenously, cause clotting of the blood, obliterating the vessels, and resulting in rapid death from heart

clots. After studying various other possible solvents for the toxic glucosid,[8] a suspension was finally settled on. It was prepared by taking the desired dose of toxin dissolved in absolute alcohol, and mixing it with freshly sterilized distilled water (0.5 to 2 c.c.). This yields a suspension of the toxin so fine that it does not separate after standing for several months. The addition of normal saline solution, however, does cause it to precipitate inside of forty-eight hours. That this suspension is still toxic was proved by tests on my arm. Such a suspension is readily and safely introduced into the blood-stream without causing clotting or death in the doses used.

TABLE 5.—INTRAVENOUS INJECTIONS OF RABBITS WITH SUSPENSION OF RHUS TOXIN

Rabbit No.	Weight, Gms.	Toxin, Gms.	Alcohol, c.c.	Water, c.c.	Time Observed, Days	Result
10	2360	.003125	.125	.375	5	Negative
10	2280	.003125	.125	.375	6*	Negative
10	2180	.0125	.5	.5	5*	Negative
10	2260	.0125	.5	.5	8*	Negative
12	1650	.025	1.	2.	30	Negative
16	2410	.0228	1.	2.	30	Gained weight
16	2675	.0228	1.	1.	11*	Dead; pleuro-pneumonia; no nephritis.
15	2300	.0456	2.	2.	23	Negative
13	2170	.0684	3.	2.	30	Site necrosed
18	1700	.0456	2.	1.	..	Died immediately

*Days additional.

The suspension was also given to guinea-pigs, subcutaneously, as shown in Table 6, without deaths from the toxin, though it caused induration and necrosis at the site of injection.

TABLE 6.—SUBCUTANEOUS INJECTION OF GUINEA-PIGS WITH SUSPENSION OF RHUS TOXIN

Pig No.	Weight, Gms.	Toxin, Gms.	Alcohol, c.c.	Water, c.c.	Days Observed	Result
12	470	.0125	.5	.75	21	Slight induration
13	330	.0125	.5	.75	21	Slight induration
14	500	.025	1.0	1.5	17	Induration and necrosis
15	280	.03875	1.5	3.5	12	Induration and necrosis
16	300	.0228	1.0	1.	33	No nephritis. Necrosis. Died
17	430	.0456	2.	1.	29	No nephritis. Necrosis. Died.

8. The toxin is insoluble in glycerin or in rabbit serum.

COMPARISON OF DOSAGE

In my extraction of the rhus plants, I found that the plant yields in pure toxin about 1/1,000 of its weight. One c.c. of the fluid extract used represents 1 gm. of the plant. From these data it is assumed that 1 c.c. fluid extract contains 0.001 pure toxin. But the fluid extract is made by extracting the plant with 65 per cent. alcohol, whereas I used 95 per cent., which extracts much more toxin. The disparity of toxicity was also clearly demonstrated by tests on my arm. So that while the above dosage appears small, the toxicity as compared with the fluid extract is satisfactory. Thus while Ford found 0.25 c.c. fluid extract fatal for a 250 gm. guinea-pig, the dose in terms of pure toxin, 0.0031 gm., or .0000123 gm. toxin per gram weight of pig, is very much smaller than I was able to give—0.03875 gm. or .0001385 gm. toxin per gram weight of pig, as illustrated by Guinea-Pig 15, Table 6. And even in terms of fluid extract, if one might assume that the extract Ford used was of equal toxicity to mine, I was able to give a larger dose, as illustrated by Guinea-Pig 9, Table 1. The doses I used were not fatal, the deaths occurring from intercurrent diseases, and showing no nephritis.

CUTANEOUS TESTS

From clinical observation of human cases, and from the internal administration to animals,[2] the toxin appears to have a selective action for epithelial cells. For this reason it is customary to experiment on the cutaneous surfaces of animals. Observations of this character indicate clearly that individuals of the same species vary widely in their susceptibility to rhus poisoning, as witnessed by the following experiments on rabbits and a monkey (Table 7). Of ten rabbits tested by applying rhus poison to shaved spots on the outer surface of their ears, seven failed to develop any dermatitis at all. Although the pure toxin was applied thoroughly to the thin skin of the monkey, the test was absolutely negative, observed for one month.

TABLE 7.—RESULTS OF APPLYING RHUS TOXIN TO THE SKIN OF ANIMALS

Rabbit No.	Materials Used	Time Observed Days	Result
1	Fluid extract	90	Negative
3	Pure toxin	18	Negative
5	Pure toxin	14	Negative
4	10 per cent. tinct.	14	Negative
2	Green leaves	2	Positive
6	Pure toxin	14	Positive
4	Pure toxin	5	Positive
11	Alcohol sol. toxin	14	Negative
18	Alcohol sol. toxin	14	Negative
17	Alcoholic sol. toxin	14	Negative
Monkey.	Pure toxin (left eyelid and chin)	30	Negative

THE ANTIGENIC PROPERTIES OF RHUS TOXIN

The possibility of producing an antitoxic serum is so attractive that special study was made as to the possibility of artificial immunization of animals. My experiments on this point indicate clearly that the toxin is not in itself fatal for rabbits and guinea-pigs, and, therefore, no antitoxic action of an immune serum could be tested on these animals. It is, however, well known, that the Bordet-Gengou fixation reaction serves to detect antibodies in an immune serum and the demonstration of such substances was sought for in rabbits that had received several doses of the toxin. The test was made with the sera of three animals, treated as follows:

TABLE 8.—RABBIT 19. IMMUNIZATION. INTRAVENOUS INJECTIONS OF SUSPENSION OF RHUS TOXIN

Date	Weight, Gms.	Toxin, Gms.	98 Per Cent. Alcohol, c.c.	Water c.c.	Results
Aug. 6	1920	0.0228	1	1	Normal
Aug. 9	1980	.....	..	..	Edema of ear
Aug. 10	2040	0.0228	1	1	
Aug. 14	2020	.....	..	..	
Aug. 16	1970	0.0228	1	1	
Aug. 20	2030	0.0228	1	1	Large necrosis of ear
Aug. 27	....	.....	..	..	Bled to death for serum

TABLE 9.—RABBIT 15. IMMUNIZATION. INTRAVENOUS INJECTION OF SUSPENSION OF RHUS TOXIN

Date	Weight, Gms.	Toxin, Gms.	98 Per Cent. Alcohol, c.c.	Water c.c.	Results
Aug. 10	2190	0.0228	1	1	Normal
Aug. 14	2260	0.0228	1	1	
Aug. 16	2230	0.0228	1	1	
Aug. 20	2180	0.0228	1	1	Large necrosis ear
Aug. 25	....	.....	..	..	Littered six
Aug. 27	....	.....	..	..	Bled to death for serum

TABLE 10.—RABBIT 13. INTENSIVE IMMUNIZATION. INTRAVENOUS INJECTION OF SUSPENSION OF RHUS TOXIN

Date	Weight, Gms.	Toxin, Gms.	98 Per Cent. Alcohol, c.c.	Water c.c.	Results
Aug. 10	2190	0.0456	2	2	Normal
Aug. 14	2160	0.0228	1	1	Normal
Aug. 15	2150	0.0228	1	1	Edema of ears
Aug. 16	2140	0.0228	1	1	
Aug. 20	2160	.....	..	..	Large necrosis ear
Aug. 24	2180	.....	..	..	Bled to death for serum

With the sera from these supposedly immunized animals, viz.: Rabbits 19, 15 and 13, the fixation test was done as indicated in the experiment shown in Table 11, which includes appropriate controls.

TABLE 11.—RESULTS OF FIXATION TESTS WITH SERUM FROM IMMUNIZED ANIMALS*

Tube No.	Rhus Antigen, c.c.		Immune Serum 56°, c.c.		c.c.		Hemolysis
1	"x"	1	No. 19,	0.3	Alexin,	0.1	+ 25 minutes
2	"y"	1	No. 10,	0.3	Alexin,	0.1	+ 15 minutes
3	"z"	1	No. 19,	0.3	Alexin,	0.1	+ 15 minutes
4	"x"	1	Norm. Rab.	0.3	Alexin,	0.1	+ 25 minutes
5	"y"	1	Norm. Rab.	0.3	Alexin,	0.1	+ 15 minutes
6	"z"	1	Norm. Rab.	0.3	Alexin,	0.1	+ 15 minutes
7	Saline	1	No. 19,	0.3	Alexin,	0.1	+ 15 minutes
8	"x"	1	Saline	0.3	Saline	0.1	0
9	"y"	1	Saline	0.3	Saline	0.1	0
10	"z"	1	Saline	0.3	Saline	0.1	0
11	"x"	1	No. 15,	0.3	Alexin,	0.1	+ 15 minutes
12	"y"	1	No. 15,	0.3	Alexin,	0.1	+ 15 minutes
13	"z"	1	No. 15,	0.3	Alexin,	0.1	+ 15 minutes
14	"x"	1	No. 13,	0.3	Alexin,	0.1	+ 18 hours
15	"y"	1	No. 13,	0.3	Alexin,	0.1	+ 1 hr. 15 min.
16	"z"	1	No. 13,	0.3	Alexin,	0.1	+ 1 hour
17	Saline	1	No. 15,	0.3	Alexin,	0.1	+ 15 minutes
18	Saline	1	No. 13,	0.3	Alexin,	0.1	+ 1 hour

*Incubated 37° one hour; then added to each tube 1 c.c. 5 per cent. saline suspension sheep corpuscles, sensitized; incubated 1½ hours.

Note: Antigen=Suspension of *Rhus diversiloba* toxin in normal saline, made from saturated alcoholic solution of toxin, in following proportions:

"x"=5 per cent. saturated alcoholic solution with normal saline.

"y"=.5 per cent. saturated alcoholic solution with normal saline.

"z"=.05 per cent. saturated alcoholic solution with normal saline.

Alexin=Normal guinea-pig serum, 18 hours old, 10 per cent. in normal saline.

It is seen that these hemolytic tests failed to demonstrate the presence of antibodies by the Bordet-Gengou method in the sera of rabbits that had received repeated doses of the toxin. *The conclusion suggested is that attempts to demonstrate antibodies in rabbits treated with rhus toxin are futile.* This does not exclude the possibility of tissue immunity. Nevertheless, contrary to the reported experience of others, I am still as sensitive to poison oak as ever, though I have been severely poisoned, accidentally, on many occasions, and have poisoned limited areas experimentally a great many times.

THERAPEUTIC TESTS

In addition to the above investigations into the nature and action of the toxin, some observations and experiments were made testing therapeutic and prophylactic measures. Two methods were employed in studying therapy; some persons were poisoned in the usual accidental way by exposure to the plant in the country, and in other cases the dermatitis

was purposely induced[9] by applying the toxin, either pure or in some menstruum. The latter method is preferred because symmetrical spots can be chosen, and the usual variables in individuals eliminated. In cases of accidental poisoning the worse half of the body was selected for testing the therapeutic agent, the milder half being used for control. The prophylactic measures were tried on myself. The clinical observations detailed below serve to illustrate the methods employed, and to indicate the value of some treatments.

IMMUNE'S SERUM

While it is recognized that a person, though immune, might not yield antitoxin in his serum, still, in connection with the previous experiments in animal immunity, it was thought worth while to test therapeutically the serum of a person who shows marked resistance to the toxin. Blood was therefore taken from the "Immune" heretofore referred to as "E. F.," Experiment 10.

Experiment 13.—

Test 1: A mixture of equal parts of water, tincture rhus, and blood from E. F., an immune, was applied to my arm and knee. Dermatitis developed at each place.

Test 2: A mixture of equal parts of E. F.'s blood and tincture rhus was applied to my arm. Dermatitis developed.

Test 3: Having smeared E. F.'s blood on my arm, tincture of rhus was then applied on the same area. Dermatitis resulted.

From these tests it appears that blood from an immune contains nothing able to inhibit the toxicity of rhus.

Experiment 14 (Ammonia Water).—Equal parts of ammonia and tincture rhus were mixed and tested on the skin. The mixture is toxic, from which it is evident that ammonia does not destroy the poison.

Experiment 15 (Peroxid of Hydrogen).—Because it is a strong oxidizer, it was presumed that hydrogen peroxid would have some curative property. But when tested by adding it in equal quantity to the rhus tincture, it failed to inhibit the toxicity, and when tested, with control, on a patch of dermatitis it was found inert.

Experiment 16 (Aristol).—The left of two artificial patches of dermatitis was treated during five days with a solution of aristol in cotton-seed oil. The control received no treatment. Both were scratched. Result: The *untreated* patch recovered first.

Experiment 17.—The same test was made on the left of two spots produced by green leaves. The aristol in oil was applied five times in four days and protected by gauze held in place by plaster. Result: No difference could be noted. Aristol therefore appears to be of no value.

Experiment 18 (Castor Oil).—A mixture of equal parts of 10 per cent. tincture of rhus and castor oil was rubbed on the arm. In thirty-six hours there was a slight itching, but no eruption.

Experiment 19 (Cedar Oil).—A similar mixture with cedar oil was applied to the arm. After thirty-six hours, a slight eruption appeared which later developed into a fair patch of itching dermatitis.

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9. In all human skin tests the author was the subject, except where otherwise mentioned; and the toxin always from *Rhus diversiloba*, except where otherwise stated.

Experiment 20 (*Cotton Seed Oil*).—A similar mixture with cotton seed oil was applied to the thin skin at the wrist. After eight days no dermatitis had appeared.

Experiment 21.—Cotton seed oil in which green leaves had been soaked for twenty-four hours was applied to the arm. The result was a slight dermatitis. This, repeated on another person, gave the same result.

Experiment 22.—Some cotton seed oil in which green leaves had been heated was applied to the arm. After four days, itching began, and in five days, a slight eruption.

Experiment 23.—A mixture of equal parts of tincture of rhus and cotton seed oil was applied to the arm. No dermatitis was detected in eight days.

These results raised the question whether cotton-seed oil did not combine chemically with the toxin, destroying the toxicity. To test this point, the mixture of oil and tincture was allowed to stand a few days when the tincture formed a layer above the oil. This supernatant fluid was toxic, producing dermatitis.

Experiment 24.—A mixture of equal parts of tincture rhus and of tincture of green soap was applied to the arm and protected by gauze. After twenty-four hours only a slight eruption was noted.

Experiment 25.—A mixture of tincture of rhus, 25 parts, and tincture of green soap, 5 parts, was applied to arm and protected with gauze. Only slight dermatitis resulted.

Experiment 26.—After allowing tincture of green soap to dry on a spot, tincture of rhus was applied. A control spot was made with the rhus alone. Both spots were protected with gauze. The control took well, while the soaped spot showed a slight dermatitis. Thus it appears that soap deters the poison of rhus.

Experiment 27 (*Ichthyol Collodion*).—The worse of two patches of dermatitis, three days old, was painted with a 5 per cent. ichthyol collodion daily. In twenty-four hours distinct improvement was noted in the treated patch, and this patch recovered earlier. This was confirmed in treating hospital cases.

Experiment 28 (*Hyposulphite of Sodium*).—Tests with this substance were also negative. It failed to inhibit the toxicity when added in large proportion to the tincture of rhus; and it failed to show curative effect on dermatitis patches compared with controls.

Experiment 29 (*Iodid of Potassium*).—This substance in strong solution, added to an equal part of tincture rhus, failed to inhibit the toxicity as tested on the skin.

Experiment 30 (*Tincture of Iodin*).—Full officinal strength tincture of iodin when mixed with an equal quantity of tincture of rhus *destroys the poison;* for when this mixture is tested on my arm no dermatitis results. If, however, the strength is reduced to less than 5 per cent. of the mixture, by addition of water or alcohol, the toxicity is not destroyed completely.

Experiment 31.—Tincture of iodin also has curative property. To one of two patches of dermatitis, officinal tincture of iodin was applied. The application burned. But the treated patch recovered earlier than the control. Itching quickly subsided and healing followed. The spot remained discolored, and tender, presumably from iodin burning.

Experiment 32.—The right of two patches of dermatitis was rubbed with 90 drops of water mixed with 10 drops of tincture of iodin. The control was rubbed with alcohol. The application of iodin caused a burning sensation, not severe. In twenty-four hours the rhus dermatitis had disappeared, but was replaced by an iodin burn. The control ran a normal course.

Experiment 33 (*Potassium Permanganate*).—A mixture of equal parts of potassium permanganate (0.56 gm. in 120 c.c.) with tincture rhus, when tested on the arm was found to be absolutely non-toxic.

Experiment 34.—One of two patches of dermatitis was painted with potassium permanganate in the above strength. The treated patch healed earlier than the control.

Experiment 35 (*Magnesium Sulphate*).—Chemical Tests: A fresh rhus leaf macerated with a saturated solution of magnesium sulphate remained toxic, as proven by testing on my arm.

Experiment 36.—Saturated solution of magnesium sulphate (Squibb's), added in equal quantity to tincture rhus, does not inhibit the toxicity, for dermatitis results when the mixture is applied to the skin.

THERAPEUTIC TESTS

Though magnesium sulphate fails to destroy the toxicity of rhus when mixed with its tincture, or its juice, it nevertheless possesses definite therapeutic value.

Experiment 37.—Test 1: In one of two patches of dermatitis, saturated solution of magnesium sulphate was rubbed three times at hour intervals. By the next morning the treated patch was better than the control. Three more similar applications were made during the forenoon and by noon a very marked improvement was noted. The treated patch recovered earlier than the control.

Test 2: To one of two patches of dermatitis, saturated solution of magnesium sulphate (Squibb's) was applied on gauze, covered with rubber tissue, and a bandage. A similar dressing was applied to the control, using water in place of magnesium. After twenty-four hours, while the first patch was not healed, it was free from itching, was not tender, and not edematcus, thus contrasting with the control, which remained tender for six days.

HOSPITAL CASES

A. B., male, aged 23, was poisoned four days previously. Whole face was edematous and the right eye closed. On Oct. 25, 1911, in the afternoon, hot applications of 2 per cent. permanganate were begun, but applied only to the right side of the face. In thirty hours the right eye was in good condition. The left side recovered tardily.

B. C., male, March, 1912, face and hands severely poisoned. The right side of the face and the right arm were treated with the hot permanganate, while the opposite side was treated with hot standard photographer's solution of sodium hyposulphite. In addition, both arms were bandaged in their respective solutions. After twenty-four hours the patient stated that the permanganate side felt distinctly better than the other. The right side recovered the earlier.

E. U., male, aged 25, was poisoned four days previously. Both arms showed marked edema, vesicles and pustules. He had already applied cold permanganate six or seven times. Hot permanganate was applied frequently by the nurse. There was no improvement in forty-eight hours. When the solution was changed to hot mercuric chlorid, and bandaging begun with the same, recovery began.

This case illustrates the uselessness of permanganate when the vesicles become infected.

A. E., male, aged 45. Dermatitis one day old. The whole face was swollen. The eyes half closed by edema of both lids. The right ear was much swollen. Thirty hours after the dermatitis began, hot permanganate saturated solution was applied to all areas. The application burned severely, especially the eyelids. Recovery occurred in five days, though this man had always been two weeks getting well. A weaker solution of permanganate would have been better.

There are two objections to the use of potassium permanganate. It produces a mahogany brown stain, at times difficult to remove. However, a 1 per cent. solution of oxalic acid is usually sufficient to disperse the stain. It should not be forgotten that this acid, internally, is a violent poison, and should be used with great caution. The other objection is that after its use, followed by oxalic acid, the skin is left severely cracked, which is especially disagreeable on the face and hands. This is met by soothing ointments or oils.

PROPHYLAXIS

I have frequently protected myself against poisoning, as have others, when not in direct contact with the plant, by simply washing the exposed surfaces within a few hours after exposure, using soap and hot water. When, however, I am to be thoroughly exposed, as in gathering the leaves or handling the dried plants, I prefer the protection of cotton-seed oil on hands, arms and face, gloves, a bath for the whole body as soon after exposure as possible, and a change of clothing.

TREATMENT

Inasmuch as the poison, after alighting on the skin, takes some time to penetrate, the first thing to do is to prevent penetration by a soap and hot-water bath of the whole body, including the hair. No article of clothing should be donned that has been exposed to the poison. Itching is readily relieved by water as hot as can be borne, and is usually a pleasant treatment, and of itself assists cure. The remedies previously discussed may then be used. If pustules have formed, the condition of bacterial infection must be recognized and will alter treatment, as illustrated by hospital case, E. U.

CONCLUSIONS

The toxic principle of rhus, while non-volatile, can poison at a distance by means of mechanical carriers. It is not destroyed by subjection for one hour to 100 C., and is carried, potent, by the smoke from burning rhus plants. The dermatitis is purely a local affection, and is not spread by the blood or lymph, or by the serum of the blebs. The sweat reaction has no relation to susceptibility. Absolute immunity in man is improbable, and experimental immunity in animals is not yet demonstrated. A permanent aqueous suspension of the alcoholic solution of the toxin can be prepared and remains toxic; this is precipitated by salt. As much as 0.025 gm. toxin can be given intravenously in aqueous suspension to a 2,000 gm. rabbit without fatal effect; and as much as 0.03875 gm. can be given to a 280 gm. guinea-pig subcutaneously without fatal effect.

Inasmuch as animals cannot be killed by the pure toxin, it is impossible to demonstrate antitoxic effect by the serum of animals that have received repeated doses of the toxin. The Bordet-Gengou fixation reaction failed to demonstrate the presence of antibodies in the sera of animals so treated.

The simplest prophylactic measure against rhus poisoning is to wash well with soap and hot water as soon after exposure as possible. The protection of the skin by anointing with cotton-seed oil before exposure, and washing this off within a few hours with soap and water, renders prophylaxis fairly certain. The following remedies have therapeutic value: hot water, ichthyol collodion, potassium permanganate, magnesium sulphate and tincture of iodin.

I gladly acknowledge my lasting obligation to Dr. F. P. Gay, Dr. G. Y. Rusk, and Dr. Chas. B. Bennett of the University of California for their valuable advice and help.

EXPERIMENTAL EOSINOPHILIA WITH AN EXTRACT OF AN ANIMAL PARASITE

ITS RELATION TO ANAPHYLAXIS AND CERTAIN CLINICAL PROBLEMS *

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The functions of the eosinophil cells remain one of the mysteries of biology. Our knowledge of these cells includes their morphology, their place of origin and the naming of the various clinical conditions in which their number either in circulating blood or locally in the tissues varies from the usual. Of the rôle played by the eosinophil leukocytes in the economy of the body we know little. Experimental work has lagged far behind speculation in this field.

Some months ago a phase of the problem of the functions of the eosinophil cells was suggested by two observations. In 1910 a case of bronchial asthma came to my notice showing extreme blood-changes—a leukocytosis of 56,000, an eosinophilia of 77 per cent.[1] This was placed on record together with a review of the literature of this well-known feature of asthma. At about the same time Goldschmidt[2] recorded the observation that laboratory workers whose duties led them to dissect *Ascarides* became sensitized so that tenderness and swelling of the fingers, conjunctivitis, coryza, sneezing, cough and asthmatic attacks resulted, and became increasingly severe with repeated handling of the material. It was found that the asthmatic attacks had a remarkable periodicity and in some instances persisted two weeks after cessation of contact with the worms.

Several baffling problems are linked, however complexly, by these observations. Common to both bronchial asthma and *Ascaris* infestation is an increase of the eosinophils of the blood. One may well ask the significance of the eosinophilia in this association. Further, it has been suggested that asthma may be classified among the phenomena of anaphylaxis.[3] Many of the reflex and toxic symptoms seen clinically in

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1. Herrick, W. W.: The Eosinophilia of Bronchial Asthma, with Report of a Case Showing Extreme Blood Changes. Jour. Am. Med. Assn., 1911, lvii, 1836.

2. Goldschmidt: Die Ascarisvergiftung. München. med. Wchnschr., 1910, lvii, 1991.

3. Meltzer: Bronchial Asthma as a Phenomenon of Anaphylaxis. Jour. Am. Med. Assn., 1910, lv, 12, 1020.

Ascaris infestation have been assigned to the same category.[4] Is, then, the eosinophilia of the blood present in most instances of either of these conditions the result of specific sensitization or anaphylaxis? If this eosinophilia can be explained on such a basis, exactly what are the substances responsible for this effect and under what conditions is such effect produced?

As such a study involves of necessity experimental eosinophilia with animal parasites or their products, it may be well to review the subject briefly.

REVIEW OF LITERATURE

Calamida[5] prepared from the *Tenia cucumerina* and the *Tenia coenurus* of the dog a concentrated extract which he claims has a chemotactic effect on the eosinophils. A capillary tube containing this extract placed in the peritoneal cavities and subcutaneous tissues of rabbits was found at the end of twenty-four hours to contain many leukocytes, most of which were eosinophils. The most thorough study of the eosinophil leukocytes is that made by Opie[6] in 1904. Working with guinea-pigs, Opie produced trichiniasis by feeding infected meat and noted a striking rise in number of eosinophil cells in the blood at the end of the second week after infection. This eosinophilia reached its maximum at the end of the third week. In the lungs and mesenteric glands of the infected animals, masses of eosinophil cells were observed replacing polymorphonuclear neutrophils and resembling small abscesses. This increase in the eosinophils was accompanied by characteristic changes in the bone-marrow—a diminution of fat and a replacement of this tissue by cellular elements, prominent among which were immense numbers of cells with eosinophil granulations, many showing mitoses. Opie is in accord with Ehrlich in the opinion that the bone-marrow is the seat of multiplication of the eosinophil leukocytes. Infection with a large number of *Trichinellae* caused diminution in the number of eosinophils and was quickly fatal. In general, a mild infection seemed to stimulate the eosinophil cells to rapid multiplication; a severe infection caused their destruction. Opie noted a remarkable relation between the nutrition of the guinea-pigs and the numbers of eosinophils in the circulating blood. The animals below 500 gm. in weight had an average eosinophilia of 2 per cent.; those above this weight quite constantly a larger number of these cells. A

4. This has been suggested by Moschcowitz: Eosinophilia and Anaphylaxis. New York Med. Jour., 1910, xciii, 15, and others.

5. Calamida: Weitere Untersuchungen über das Gift der Tänien. Centralbl. f. Bakter. u. Parasit, 1901, xxx, 374.

6. Opie: The Occurrence of Cells with Eosinophil Granulation and Their Relation to Nutrition. Am. Jour. Med. Sc., 1904, cxxvii, 2, 217: also An Experimental Study of the Relation of Cells with Eosinophil Granulations to Infection with an Animal Parasite, *ibid.*, 1904, cxxvii, 3, 477.

periodic variation in the number of eosinophils was shown by many animals. Starvation caused prompt fall in the number of eosinophil leukocytes and with gain in weight their numbers again rose.

Proscher[7] produced local eosinophilia by the intraperitoneal injection of an extract of *Tenia solium*, finding that after an interval of five to forty minutes the polynuclear neutrophils in the peritoneal fluid about the site of injection were replaced by eosinophils. Proscher and Pappenheim[8] injected an extract of *Tenia saginata* into the veins of rabbits and noted a resulting eosinophilia of the blood. Stäubli[9] has repeated a part of the work of Opie. This observer infected guinea-pigs with the *Trichinella spiralis* and noted the consequent eosinophilia after a period of eight days or more. He found that the eosinophil increase persisted as long as three and one-half years, that the eosinophil-producing substance did not traverse the placenta and that offspring of animals showing eosinophilia do not have this characteristic of their blood-picture. Stäubli also showed the diminution of the number of these cells during the entire time the organism is under the influence of bacterial products and the existence of a reciprocal relationship between the eosinophil leukocytes and the polymorphonuclear neutrophils.

OBJECTS OF AUTHOR'S STUDY

The problems toward the solution of which I have attempted to contribute are as follows: 1. Whether eosinophilia of the blood could be produced experimentally by the use of an extract of *Ascaris lumbricoides*. 2. Under what conditions of administration of this extract such eosinophilia might be brought about. 3. Whether or not the substance influencing the eosinophils is a protein. 4. Whether such eosinophil increase bears any relation to specific sensitization or anaphylaxis. Throughout the work the possible relation of these questions to the clinical problem of bronchial asthma has been constantly in mind.

EXPERIMENTAL WORK

Guinea-pigs were chosen for the experiments, since the blood-cells of these animals resemble rather closely those of man in morphology and in reaction to bacterial and other agencies. For convenience the fine granular polymorphonuclear amphophils of the guinea-pig are termed polynuclears. It is important to have clearly in mind the usual blood-picture

7. Proscher: Ueber experimentelle Erzeugung von eosinophile Exsudaten. Fol. Haematol., 1905, ii, 543.

8. Proscher and Pappenheim: Ueber experimentelle Leucocyten. Fol. Haematol., 1904, i, 638.

9. Stäubli: Trichinosis, 1909, p. 107 et seq.; also Die klinische Bedeutung der Eosinophilie, Ergebn. d. inn. Med. u. Kinder., 1910, vi, 12 and Ueber Eosinophilie, Samuel. klin. Vortr., 1909, clxvii, 43.

of the guinea-pig. Gulland and Goodall[10] give as an average the following count of leukocytes: Number in a c.mm., 10,500; polynuclears, 43 per cent.; lymphocytes, 52 per cent.; eosinophils, 2.5 per cent.; basophils, 2.5 per cent. Kurloff, quoted by Opie from Ehrlich and Lazarus, states that the average percentage of eosinophils is 1. Kanthack and Hardy[11] give 2 per cent. to 3 per cent. as the average figures. Opie's figures are higher. In counts of 10 guinea-pigs the average percentage of eosinophil leukocytes was found to be 11. I have averaged the counts of seventeen animals before experiments were begun and find the following figures: Leukocytes, 10,341; polynuclears, 34.5 per cent.; large lymphocytes, 2.5 per cent.; small lymphocytes, 59.5 per cent.; eosinophils, 2.5 per cent.; basophils, 1 per cent.; total number of eosinophils in 1 c.mm., 363. In making the counts recorded in this work the blood was taken from the ear, a pipet giving a dilution of 1 to 20 and the Zappert counting chamber were used. Smears were made in the usual way, stained by Wright's stain, and 200 cells counted.

The extract used was prepared from the *Ascaris lumbricoides* of the pig. The fresh worms were washed in distilled water, finely divided, then ground with sand in a mortar and sufficient 0.5 per cent. sodium chlorid solution added so that each c.c. of the decanted solution represented 1 gm. of the fresh material. The solution was passed through a Berkefeld filter and to it was added 0.5 per cent. phenol, a preservative having on intraperitoneal injection no effect on the numbers of eosinophils or basophils of the guinea-pig (Schlecht[12]). This extract, kept on ice, was a slightly turbid yellowish liquid, having the acrid odor characteristic of the *Ascarides* and containing protein in considerable amount. Injected intraperitoneally in guinea-pigs peritonitis did not follow, nor did any direct toxic effects result from the rather small quantities—2 to 5 c.c.—used. It may be of interest to record that, notwithstanding having worked with *Ascarides* and their extracts at intervals for more than a year and a half, neither the laboratory *diener* nor myself has shown symptoms of sensitization.

Taking up in their order the problems suggested, report is given of a selected number of such experiments with the fifty-six animals used as have bearing on their solution.

There can be no question that increase in the eosinophils of the blood of guinea-pigs may be produced experimentally by the intraperitoneal

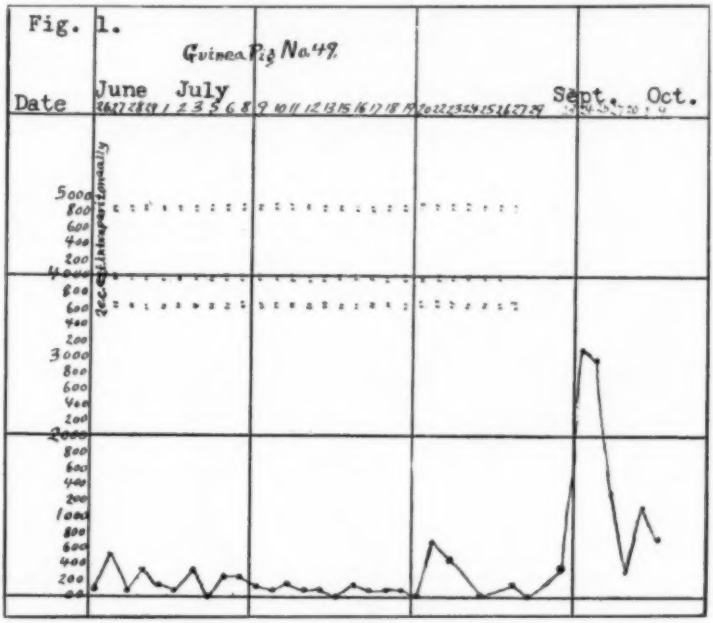
10. Gulland and Goodall: The Blood, 1912, p. 76.

11. Kanthack and Hardy: Wandering Cells of Mammalia. Jour. Physiol., London, 1894, xvii, 81.

12. Schlecht: Ueber die Einwirkung von Seruminjectionen auf die Eosinophilen und Mastzellen des menschlichen und tierischen Blut. Deutsch. Archiv f. klin. Med., 1910, xcviii, 308.

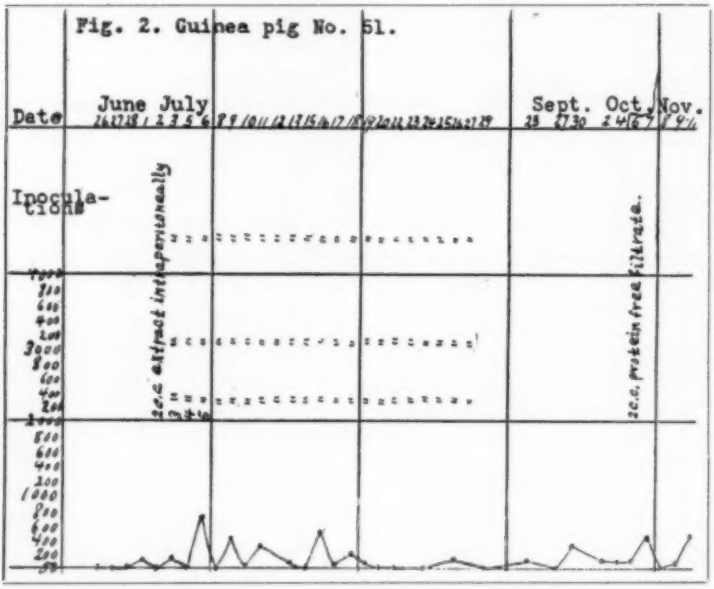
injection of an extract of *Ascaris lumbricoides*. In each instance in which this phase of the problem was investigated a positive result was obtained. (Experiments with Guinea-Pigs 34, 36, 46, 47, 48, 49, 53.)

The methods of administration of the extract bringing about such increase in the number of eosinophils are of particular interest. As to dosage, a comparatively small amount of material is effectual when introduced into the peritoneal space of guinea-pigs; 2 c.c. of the extract was used in all but a very few instances. Where larger amounts—never more than 5 c.c.—were employed this is noted on the charts. The larger amounts seemed not to influence results in any way differing from the



smaller dosage; the increase in number of eosinophils bearing no relation to the amount of extract administered. The factor of greatest influence in the production of this eosinophilia was the interval between injections of the extract. Injections of 2 to 5 c.c. daily over a period of four weeks was without influence on the eosinophil content of the blood of guinea-pigs (Fig. 1, Guinea-Pig 49; and Fig. 2, Guinea-Pig 51.). Injections of 2 c.c. of the extract every second or every third day was also without result (Fig. 3, Guinea-Pig 46.). Two series of injections daily or every second or third day, the two series being separated by an interval of ten days, was accompanied during the second series by but slight rise in the

number of eosinophils (Fig. 3, Guinea-Pig 46.). Injections of the extract at intervals of five to twenty-five days was followed without exception by a striking increase in the eosinophils of the blood (Figs. 4, 10, 6 and 9; Guinea-Pigs 45, 34, 47 and 53.). A series of injections followed after an interval of two to eight weeks by a further single injection had as a sequel a striking increase in the number of eosinophils (Guinea-Pigs 36, 46 and 49; Figs. 7, 3 and 1.). In no instance was a first injection followed by an eosinophil increase. Each single reinjection when separated from the preceding by an interval of five days or more was followed by a more prompt response in the way of an eosinophil increase (Guinea-Pigs 34,



45 and 47; Figs. 10, 4 and 6), and in some instances each successive response was more marked (Guinea-Pigs 45, 47 and 48; Figs. 4, 6 and 8.). Exceptions to this may be noted in the charts, but to illustrate the average tendency in these particulars I have made a composite chart by averaging the blood-counts of four animals having interval injections (Fig. 5).

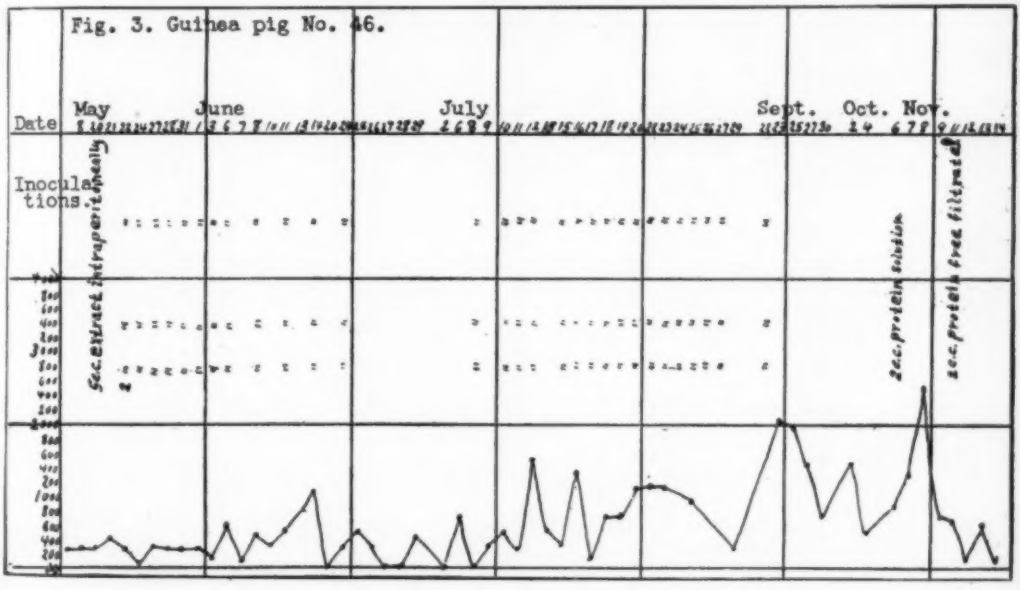
The most pronounced eosinophilia in the series was observed in Guinea-Pig 36 (Fig. 7), in which the control count of these cells was high. Injections daily or on alternate days for a period of three weeks were followed some four weeks later by a considerable rise in number of eosinophils, which, one week after the further administration of a single

dose of 2 c.c., became enormous, these cells reaching the extremely high figure of 5,172 in a c.mm. Explanation of the course of the eosinophil curve in this animal is difficult in that the rise in number of these cells was not so prompt an effect of the injections as in the case of the other animals, the charts of which are here given. I have noted that guinea-pigs showing a high control count of eosinophils react to inoculations of extract of *Ascaris* in a manner less typical than that characterizing animals having a normal number of these cells.

NATURE OF THE SUBSTANCE PRODUCING EOSINOPHILIA

Is the substance influencing the eosinophil cells a protein?

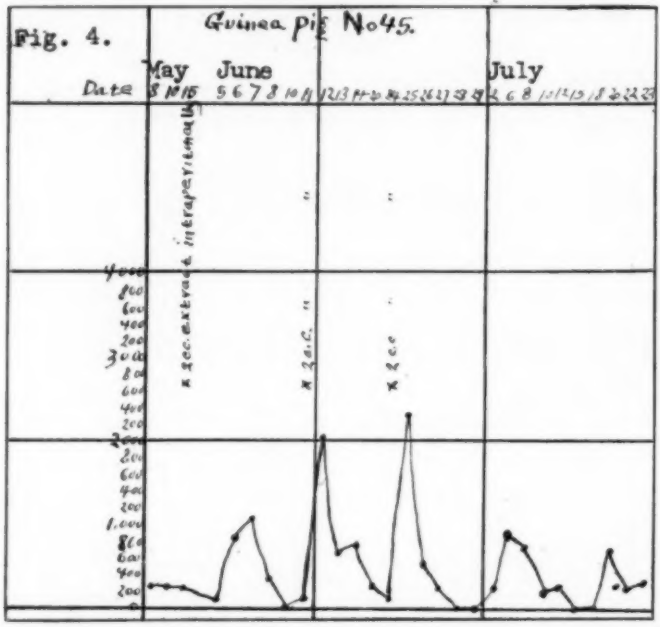
The original extract was rich in albumin, giving the biuret reaction, positive Heller's test and abundant precipitation on acidulation and



boiling. The protein was precipitated by the addition of two volumes of acetone. The abundant precipitate, isolated by filtration, was dried and dissolved in 0.5 per cent. salt solution. One gram of this precipitate was dissolved in 2 c.c. of the salt solution. This amount was injected into the peritoneal cavities of guinea-pigs previously sensitized with the original extract, death from anaphylactic shock resulting in Guinea-Pig 50, while in Guinea-Pig 46 (Fig. 3) and in Guinea-Pig 48 (Fig. 8) prompt rise in the number of eosinophils followed. Fractional precipitation of the

proteins of the extract after the method of Pick[13] was not done as the effect on the eosinophils of the intraperitoneal injection of many simple proteins has been studied by Schlecht, whose work is quoted below.

To secure an extract practically protein free, the original extract was acidulated with acetic acid and boiled, the resulting precipitate filtered through ordinary filter paper, or, in some cases, through infusorial earth and filter paper. The filtrate thus obtained gave a faint biuret reaction, but no coagulum on acidulation and heating. This filtrate injected into the peritoneal space of guinea-pigs previously sensitized with the original extract was without influence on the eosinophil cells of the blood

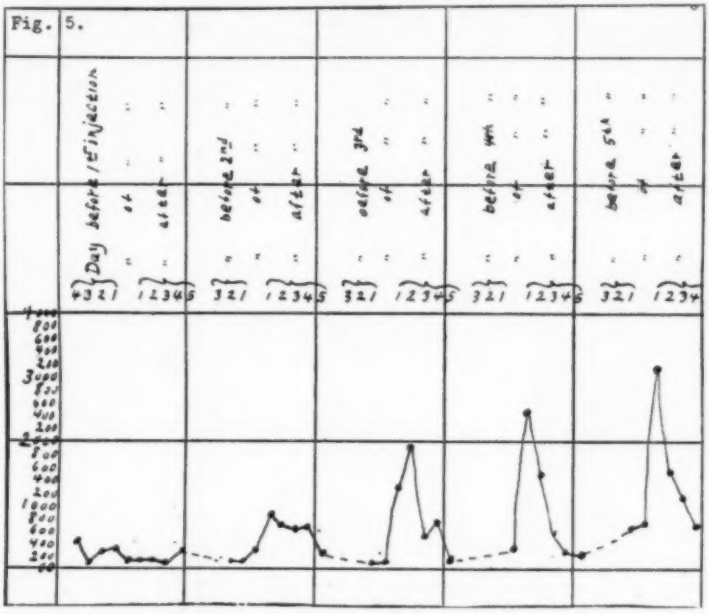


(Guinea-Pigs 46, 48 and 51). It may therefore be concluded that the protein of the *Ascaris* extract is the substance responsible for the eosinophil increase when administered by the above-described methods. This conclusion gains further proof from the work of Schlecht,[14] who, in a valuable contribution, has shown that the intraperitoneal injection of

13. Pick: Zur Kenntniss der Immunkörper; Hofmeister's Beiträge, 1902, i, 351.

14. Schlecht: Ueber die Einwirkung von Seruminjectionen auf die Eosinophilen und Mastzellen des menschlichen und tierischen Blut. Deutsch. Arch. f. klin. Med., 1910, xcviii, 308.

alien protein is followed in guinea-pigs by a striking eosinophilia of the blood. This result was obtained by the injection of whole blood-serum, egg albumin, fibrin, serum-albumin, serum-globulin and hemi-albumose; but not peptone or the products of further protein digestion—the amino acids, etc. The results obtained in my experiments with the extract of *Ascaris lumbricoides* and with the isolated protein of this extract correspond in general with those reported by Schlecht from the use of simple proteins. There is the exception that Schlecht noted the eosinophil increase following injections at intervals of less than three days when such injections were continued for a number of days.

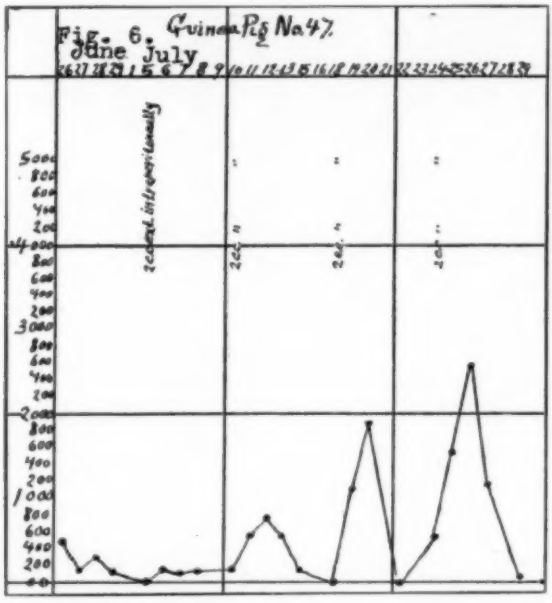


EOSINOPHILIA AND ANAPHYLAXIS

To the question, "What connection, if any, has the increase in number of the eosinophil cells of the blood noted in these experiments with anaphylaxis," no final answer can be given. However, some suggestive facts are brought out. In no instance observed did the eosinophil increase occur during a time when the animals could properly be judged immune; nor was any such increase noted during the anaphylactic shock. Immediately following the anaphylactic period the rise in eosinophils in the blood was marked and constant and more pronounced as the previous sensitization had been more thorough. Further injection of the extract

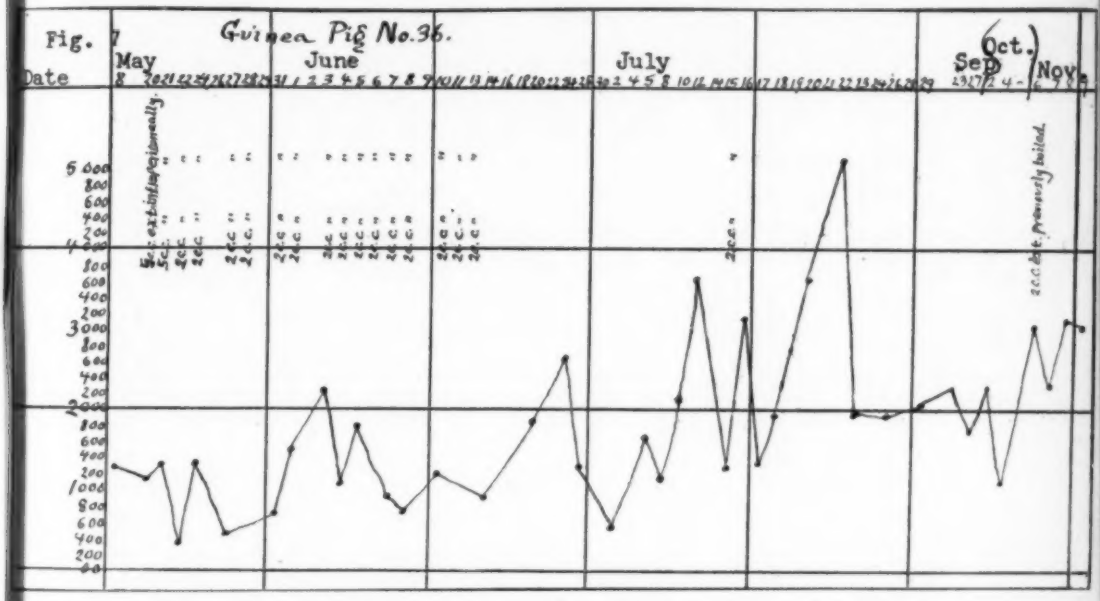
during the post-anaphylactic period was followed by a fall in the number of eosinophils (Guinea-Pig 53, Fig. 9). Eosinophilia occurred alike in the animals showing marked anaphylactic shock after their recovery (Guinea-Pigs 45 and 53, Figs. 4 and 9), and in those showing no gross evidences of this phenomenon—dyspnea, convulsions, cyanosis, paralysis, etc. (Guinea-Pigs 48 and 34, Figs. 8 and 10).

In general, it is well known that an animal surviving anaphylaxis is for a time immune, but gradually loses this immunity and again becomes sensitive to the specific protein. The eosinophil cells seem to have a direct relation to the various phases of this phenomenon. During the



period of immunity their number is not increased. It is only subsequent to the anaphylactic period, in the so-called post-anaphylactic stage that the eosinophilia appears, to vanish after twenty-four, forty-eight or seventy-two hours; after which and until the lapse of several days, these cells cannot be called out in unusual numbers. It seems probable that this does not occur until the immunity is lessened or replaced by some degree of hypersensitiveness. In the development of such immunity the eosinophil leukocytes may play a part, possibly they are the active agents in the process. This is in line with the conclusions of Schlecht,[14] who conceives of the eosinophils as cells having a special function protective against the invasion of foreign protein and designed to ward off the

danger of the anaphylactic period. Of interest in this connection is the further work of Schlecht[15] in showing that lungs of guinea-pigs dead from anaphylactic shock contain eosinophil cells in large numbers and that animals may be sensitized or may show local evidences of sensitization in the lungs by the inhalation of sprayed serum. The work of Schittenhelm, Weichardt and Grisshammer[16] claims attention in this relation. These investigators studied the effect on the blood-cells of dogs of the intravenous injection of albumin, peptone and bacterial protein, finding an immediate leukopenia, the degree of which depended not on the amount of material injected, but on its kind. Albumin injected in



sensitized animals caused a leukopenia lasting some hours and followed by a stage of leukocytosis which subsided after four to six days. This leukocytosis was mostly of the polynuclear neutrophils, but as the leukocytosis began to decline the eosinophils reached high numbers.

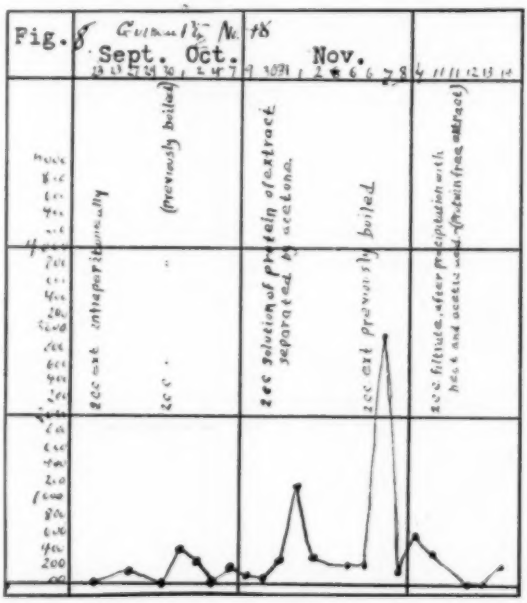
In so far as a single observation is of value, it appears that while the offspring of a sensitized animal are also sensitive to the specific protein employed, the capacity of responding by a hypereosinophilia on the injec-

15. Schlecht and Schwenker: Ueber die Beziehungen der Eosinophilie zur Anaphylaxie. Deutsch. Arch. f. klin. Med., 1912, cviii, 405.

16. Schittenhelm, Weichardt and Grisshammer: Eiweissumsatz und Ueberempfindlichkeit. Ztschr. f. exper. Path. u. Therap., 1912, x, 3, 412.

tion of the specific protein is not transmitted. That fact has an analogy in the observation of Stäubli, already cited, that the eosinophil-producing substance present in experimental trichiniasis in guinea-pigs is not transmitted through the placenta.

From the evidence presented it appears justified to conclude that the eosinophilia accompanying infestation with animal parasites is the result of protein sensitization. Exactly how this sensitization is brought about is problematical. The specific protein material may be secreted by the parasites or may be absorbed from the disintegration of those parasites perishing within the alimentary tract or in the circulation of the host.



The experimental finding that administration of an extract of *Ascaris lumbricoides* at intervals of less than five days is not followed by increase in the number of eosinophils in the blood is difficult to reconcile with clinical conditions that may reasonably be assumed to obtain in infestation with these parasites where absorption of foreign material is probably more or less continuous. Undoubtedly there are factors of which we are as yet ignorant. That a considerable latent period is necessary between the time of infection and the development of the consquent eosinophilia is apparent. This is suggested by the observations of Opie and of Stäubli, already quoted. Both found that increase in number of eosinophil leukocytes in the blood of guinea-pigs fed on meat containing

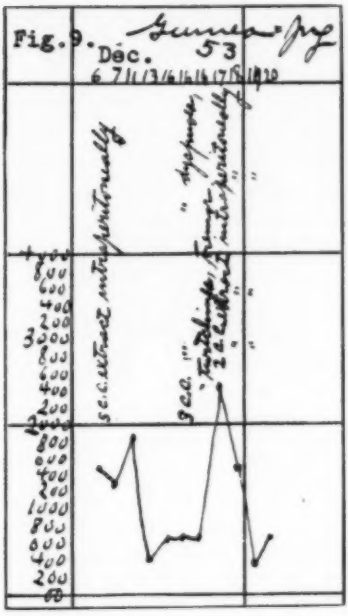


Fig. 9.
Guinea Pig
Dec. 53

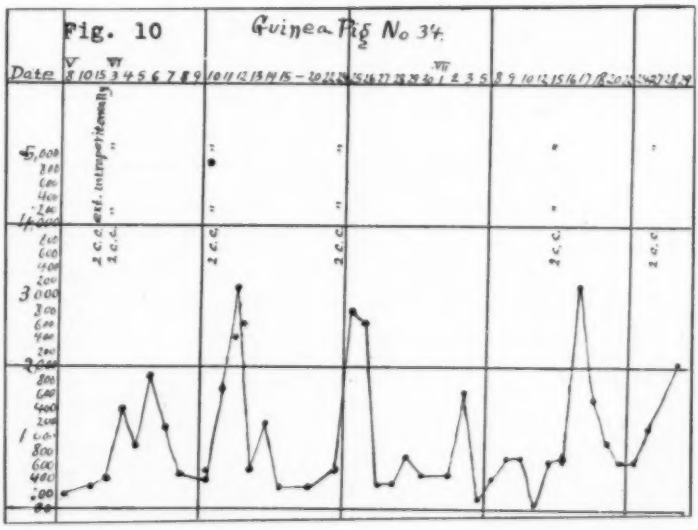


Fig. 10
Guinea Pig No 34
Date

embryos of *Trichinella spiralis* took place only after lapse of eight or more days, at a time when the embryos were migrating from the intestine to their resting places in muscle or other tissue.

It is tempting to conclude that hypereosinophilia is the result of sensitization to alien protein. This would bring into line the increase in number of these cells following injections of tuberculin, in serum sickness, many food poisonings, hay fever, the eosinophilia noted about animal parasites and other foreign protein material. Granting this, one is lured a step further to seek in sensitization to protein a cause of many types of bronchial asthma. It may be that in the discovery of some substance capable of influencing the eosinophil cells of the body we may find the key to that important clinical secret — the control of bronchial asthma.

PROTOCOLS

GUINEA-PIG 6.—May 27. Eosinophils 00. May 29, 1 c.c. extract *Ascaris* injected intraperitoneally. May 30, leukocytes 6,400; eosinophils, 00. June 6, leukocytes, 8,000; eosinophils, 00. June 9, 2 c.c. extract injected intraperitoneally, followed in ten seconds by clonic convulsions. During convulsions, leukocytes 4,000; polynuclears, 47 per cent.; mononuclears, 52.5 per cent.; eosinophils, 0.5 per cent. Partial recovery for several hours; death after six hours.

GUINEA-PIG 49.—Two c.c. extract of *Ascaris lumbricoides* injected intraperitoneally daily from June 26 to July 27 with no significant change in the eosinophil content of the blood. No injections given from July 27 to September 23, when an injection of 2 c.c. of the extract intraperitoneally gave in twenty-four hours an increase of the eosinophils from 360 to 3,040 per mm. No symptoms of anaphylactic shock.

GUINEA-PIG 51.—Weight, 417 grams. Two c.c. original extract given July 1; 3 c.c. July 3; 4 c.c. July 5; 5 c.c. July 6 and almost daily thereafter, with an occasional day excepted, until July 27. No change in number of eosinophils noted. November 6, 2 c.c. of filtrate after precipitation of albumin of original extract given intraperitoneally. (This precipitation was made by heat and acidulation with acetic acid.) No change of note in the eosinophils resulted. No signs of anaphylaxis.

GUINEA-PIG 46.—Weight, 340 grams. Five c.c. original extract given intraperitoneally May 20; 2 c.c. May 22 and on approximately alternate days thereafter to June 15. Then a single injection after ten days without effect on the number of eosinophils. July 8 to 29 injections of 2 c.c. were given daily or on alternate days with slight increase of the eosinophils. September 22, 2 c.c. extract given intraperitoneally; September 23, eosinophils, 2,010; September 30, 770.

November 6, 2 c.c. solution of protein in 0.5 per cent. sodium chlorid precipitated by acetone was given and was followed by an eosinophil increase from 860 to 1,360 in twenty-four hours; 2,511 in forty-eight hours. After seventy-two hours, eosinophils were 760. November 11, 2 c.c. filtrate of extract after coagulation of albumen with heat and acetic acid injected intraperitoneally without effect on eosinophils.

GUINEA-PIG 45.—Weight, 320 grams. Two c.c. extract intraperitoneally May 15. Slight reduction in the number of eosinophils in the blood followed. June 5, 4 c.c. extract given intraperitoneally. Severe anaphylactic shock after twenty minutes; dyspnea, cyanosis, convulsive movements, paralysis. The peripheral circulation was so affected during the shock that satisfactory specimens of blood could not be obtained. Recovery in twenty-four hours, when eosins.

were 820 in a c.mm. In forty-eight hours eosins. rose to 1,035; in ninety-six hours 400 per mm. Third injection of the extract June 11, when eosins. were 108 in a c. mm. In twenty-four hours eosins. rose to 2,030; in ninety-six hours fell to 300. June 24 eosins. numbered 110. A fourth injection of original extract given on this date was followed in twenty-four hours by eosinophil increase to 2,378. In forty-eight hours eosins. numbered 536.

GUINEA-PIG 50.—Weight, 245 grams. Control count of eosinophils 62 in 1 mm. September 23, 2 c.c. extract injected intraperitoneally. No change noted in number of eosinophils. October 30, 2 c.c. solution in 0.5 per cent. sodium chlorid of proteins of *Ascaris* extract injected intraperitoneally. Death in forty-five minutes from respiratory paralysis.

GUINEA-PIG 47.—Weight, 485 grams. Control counts of eosinophils showed variations from 0 to 438 per mm.; 2 c.c. extract injected July 5, repeated July 10. Eosinophils rose from 153 to 762 in forty-eight hours after second injection, returning to 116 per mm. the fifth day. Injection repeated July 18. Eosinophils rose from 0 to 1,817 in forty-eight hours. A fourth injection July 24 was followed in forty-eight hours by increase of the eosinophils from 504 to 2,548 per mm. In each instance the eosinophilia subsided forty-eight hours after its maximum. No evidences of anaphylactic shock.

GUINEA-PIG 36.—Weight, 460 grams. Control counts showed high eosinophilia—above 1,000 per mm.; 5 c.c. extract of *Ascaris* given for two days, then 2 c.c. daily or on alternate days from May 22 to June 13 with no change in the average number of eosinophils. July 15 a single injection of 2 c.c. of the original extract was followed by an eosinophil increase to 3,160, which after four days reached 5,172. Previous to the last injection the eosinophils on July 12 rose to 3,618, without relation to any known factor. November 6 an injection of 2 c.c. of previously boiled extract was followed by no change in number of eosinophils, which in this animal continued to be high.

GUINEA-PIG 48.—Weight, 260 grams; 2 c.c. extract given September 23; no change in eosinophils followed. September 30, 2 c.c. of the extract previously boiled given intraperitoneally and followed in twenty-four hours by a rise in eosinophils from 0 to 395 per c.mm. October 30, 1.5 c.c. of a solution in normal salt solution of the proteins of the extract of *Ascaris* precipitated by acetone was given and followed in twenty-four hours by an eosinophilia of 1,188 from one of 280. November 6, 2 c.c. of the original extract previously boiled was injected and caused an increase in eosinophils from 200 to 2,952. November 11, 2 c.c. filtrate after precipitation of albumin by heat and acetic acid was injected and was followed by no rise in the number of eosinophils; rather was there a diminution in the number of these cells—from 330 to 55 in 1 mm. No symptoms of anaphylactic shock.

GUINEA-PIG 53.—Male, weight, 675 grams. Control count showed moderately high eosinophil count, 1,456 per c.mm. December 6, 5 c.c. regular extract given intraperitoneally. No marked effect on eosinophils. December 16 these cells numbered 612 per mm. Three c.c. extract injected intraperitoneally on this date. After fifteen minutes dyspnea, tremor, slight convulsive movements. December 17, eosinophils 2,400. Two c.c. extract injected on same day. December 18, eosinophils 1,416. Two c.c. extract given. December 19, eosinophils 336. Two c.c. extract injected. December 20, eosinophils 658.

GUINEA-PIG 55.—Male, weight, 260 grams; 2 months old; offspring of guinea-pig 45. (Fig. 4.) Born Oct. 5, 1912. December 19, eosinophils 00. December 20, eosinophils 68. Five c.c. extract injected intraperitoneally. After ten minutes dyspnea, convulsions, weakness of extremities, death.

GUINEA-PIG 56.—Male, weight, 350 grams. Of same litter as No. 55. December 18, eosinophils 80; 2.5 c.c. extract injected intraperitoneally; no signs of anaphylaxis. December 19, eosinophils, 0; December 20, 0.

GUINEA-PIG 34.—Weight, 600 grams. Two c.c. extract given intraperitoneally May 15, repeated June 3 and four times additionally at intervals of one, two, three and two weeks, successively. Each injection after the first was followed by prompt rise in the number of eosinophils from 400 to 800 or to 3,192, as a maximum. In the later injections the maximal eosinophilia occurred after twenty-four hours.

CONCLUSIONS

1. A notable eosinophilia of the blood can be developed by the intraperitoneal injection of an aqueous extract of *Ascaris lumbricoides.*

2. The substance causing such eosinophil increase is a protein.

3. Previous sensitization is necessary to the development of this eosinophilia.

4. It is impossible to produce such eosinophilia while the animals are immune to the extract.

5. This eosinophilia may therefore be considered evidence of previous sensitization.

6. There is a possible association of these facts with the problem of bronchial asthma.

50 East Fifty-Third Street.

TABLE 1.—BLOOD-COUNTS IN GUINEA-PIG 49

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
June 26	9,000	47	5	45	2	1	90*
27	7,840	19.5	2	70.5	1.5	6.5	510*
28	7,200	24	3	71	1	1	72*
29	7,400	14	1	78.5	1.5	5	370*
July 1	15,800	18.5	1.5	77.5	1.5	1	158*
2	8,000	17.5	3.5	75	3	1	80*
3	9,000	17	1	76	2	4	360*
5	10,400	10.5	0.5	89	0	0	000*
6	10,400	24	1	73	0	2	208*
8	11,400	40.5	1.5	54	2	2	228*
9	5,600	18	1	78	2	1	56*
10	6,000	22	2	73.5	1	1.5	90*
11	8,200	32.5	3.5	60	2	2	164*
12	7,200	2.5	1.5	93.5	1.5	1	72*
13	8,000	13	1	85	0	1	80*
15	6,000	19	2	79	0	0	00*
16	7,600	23	1.5	64	0	1.5	114*
17	7,200	8	0.5	87.5	3	1	72*
18	8,200	13.5	1.5	82	2	1	82*
19	8,400	21.5	1	70	6.5	1	84*
20	11,800	19	1.5	78	1.5	0	00*
22	18,800	27	0	67	2	4	752*
23	8,400	26	1.5	64.5	2.5	5.5	462*
24	.....	....	....	....	....	....	.....*
25	9,800	23	0	75	2	0	.....*
26	.....	....	....	....	....	....	.....*
27	15,000	22.5	4	72.5	0	1	150*
29	6,800	26	3	71	0	0	000

TABLE 1.—Continued

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
Sept. 23	12,000	64	2.5	30.5	.00	3	360*
24	15,200	42	3	32	3	20	3,040
25	16,600	41.5	2	34.5	3.5	18.5	3,071
27	12,600	25.5	2.5	54.5	7.5	10	1,260
30	10,400	30	2	61	4	3	304
Oct. 2	13,200	41	5	46	1	7	924
4	11,600	28.5	4	60.5	0.5	6.5	744

*Two c.c. of original extract given intraperitoneally in each instance.

TABLE 2.—BLOOD-COUNTS IN GUINEA-PIG 51

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
June 26	5,000*	13.5	0.5	86	0	0	000
27	7,000	35	2	62.5	0.5	0	000
28	7,200	35	4	60	1	0	000
July 1	8,800	18.5	0.5	79	0.5	1.5	134*
2	7,000	30.5	0.5	68.5	0.5	0	000
3	9,000	19.5	1	76	1.5	2	180†
5	8,200	2	4	94	0	0	000‡
6	5,000	37	4.5	46.5	1.5	10.5	750§
8	7,400	17	1	82	0	0	000§
9	10,400	19.5	4	69	3.5	4	408§
10	14,800	48.5	2	47	2	0.5	25§
11	16,400	39	3	54	2	2	328§
12	.....	....	....	....	....	....	000§
13	20,000	14	1	84	0.5	0.5	100§
15	12,000	60	0	40	0	0	000§
16	17,000	16.5	1.5	79	0	3	510§
17	7,000	54	2.5	42.5	0	1	70§
18	6,800	29.5	1.5	65.5	0.5	3	204§
19	5,400	39.5	0	59	0	1.5	81§
20	4,900	38	4	57	1	0	000§
22	3,800	30	2	68	0	0	000§
23	.....	....	....	....	....	....	.....§
24	7,600	36	6.5	53	4.5	0	000§
25	.....	....	....	....	....	....	.....§
26	8,800	26.5	1.5	68.5	1.5	2	176§
27	.....	....	....	....	....	....	.....§
29	5,400	37	4	58	1	0	000
Sept. 23	12,400	12.5	1.5	85	0	1	124
27	10,800	30.5	2.5	66	1	0	00
30	11,000	24.5	2.5	66	4	3	330
Oct 2	15,600	14	1	83	1	1	156
4	10,200	14	4	81	0	1	102
Nov. 6	12,000	16	5	78	0	1	120¶
7	7,000	25.5	3.5	62	5	6.5	455
8	8,000	10.5	6.5	81.5	1.5	0	00
9	13,200	31.5	2.5	63.5	2	0.5	66
11	11,200	30	5	61	0	4	448

*Two c.c. original extract given intraperitoneally; †3 c.c.; ‡4 c.c.; §5 c.c.
¶Two c.c. filtrate after coagulation of albumin by heat and acidulation.

TABLE 3.—BLOOD-COUNTS IN GUINEA-PIG 46

Date		No. Leuko-cytes	Per Cent. Polynu-clears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Baso-phils	Per Cent. Eosin-ophils	No. of Eosin-ophils
May	8	11,600	37	4.5	54.5	1.5	2.5	290
	20	13,700	39	5.5	53.5	00	2	274*
	21	13,400	25	2	69.5	0.5	3	402
	22	13,400	12.5	4.5	81	0	2	268†
	24	12,400	18	1.5	80	0	0.5	62†
	27	16,000	17	2	79	0	2	320†
	28	13,200	....	....	....	....	....	.....†
	31	9,000	24	11	61	1	3	270†
June	1	12,200	22.5	5.5	69	1	2	244†
	3	9,000	19.5	2.5	76	0.5	1.5	135†
	6	12,000	35	4.5	55.5	0	5	600†
	7	14,000	25.5	4	66.5	3	1	140†
	8	22,000	15	2	79	2	2	440†
	10	11,000	31	5	60.5	1	2.5	330
	11	17,500	13	1	83	0	3	525†
	13	.....	....	....	....	....	....	.....†
	14	19,600	10.5	3.5	80	0.5	5.5	1,078
	20	9,000	16	0	84	0	0	00
	24	9,800	18	2	77	0	3	294†
	25	12,800	10	2.5	83.5	0	4	512
	26	16,000	8.5	3.5	86	0.5	1.5	240
	27	14,200	7	2	91	0	0	000
	28	12,800	19.5	0.5	78.5	1.5	0	000
	29	20,200	11	1	86	0	2	404
July	2	19,400	4	0	95	1	0	000
	6	19,800	20	3	71	2	4	732
	8	14,200	11.5	0.5	88	0	0	000†
	9	11,000	6.5	1	89	0	3.5	380
	10	10,000	29	0	65	1	5	500†
	11	17,200	6.5	0.5	91.5	0	1.5	258†
	12	11,000	5	0	81	0	14	1,540†
	13	11,000	6	2	86	1	5	550
	15	10,800	5.5	3.5	87.5	0	3.5	378†
	16	14,000	19	1	71	0	9	1,260†
	17	11,000	18	1	77	2.5	1.5	165†
	18	14,000	13	1	79	2	5	700†
	19	15,000	23.5	1.5	69.5	0.5	5	750†
	20	15,800	16.5	1.5	71	4	7	1,106†
	22	12,800	15	2	72	2	9	1,152†
	23	15,000	16	2.5	72	1.5	7.5	1,125†
	24	.....	....	....	....	....	....	.....†
	25	13,600	9	2	80	2	7	952†
	26	.....	....	....	....	....	....	.....†
	27	.....	....	....	....	....	....	.....†
	29	13,000	11	2	84	1	2	260
Sept.	22	.....	....	....	....	....	....	.....†
	23	13,400	13.5	1.5	70	0	15	2,010
	25	15,000	24	1	60	2	13	1,950
	27	10,800	28	2	54	1	15	1,620
	30	7,000	21	4	63.5	0.5	11	770
Oct.	2	17,000	16	1	72	0	9	1,460
	4	10,200	17	2	76	0	5	510
Nov.	6	17,200	24	3.5	66	1.5	5	860‡
	7	6,800	29.5	11.5	49	0	20	1,360
	8	16,200	23	6	54.5	1	15.5	2,511
	9	15,200	22	1	68	4	5	760
	11	7,200	18	2	69	2	9	648§
	12	10,200	8.5	3.5	86	0.5	1.5	153
	13	12,400	12	3	80	0	5	620
	14	9,600	8	3	87	0	2	192

*Five c.c. original extract intraperitoneally; †2 c.c. doses.

‡Two c.c. solution in 0.5 per cent. saline of protein of extract precipitated by acetone.

§Two c.c. filtrate after coagulation of protein with heat and acidulation.

TABLE 4.—BLOOD-COUNTS IN GUINEA-PIG 45

Date	No. Leuko-cytes	Per Cent. Polynu-clears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Baso-phils	Per Cent. Eosin-ophils	No. of Eosin-ophils
May 8	12,000	31	4	60	3	2	240*
10	9,400	29.5	3.5	61.5	3	2.5	235
15	11,400	32	5	59	2	2	228†
40 min. later	10,800	32	0	67	0	1	108
June 5	7,000	19.5	0	78.5	0	2	140‡
10:30 a. m.							
10:50 a. m.							
11:30 a. m.							
4:30 p. m.	8,000	63	2	27	2	6	480
June 6	16,400	28	1	65	1	5	820
7	9,000	24.5	4.5	56.5	3	11.5	1,035
8	9,600	8	2	86	0	4	384
10	8,600	13	2	85	0	0	00
11	10,800	7	3	85	4	1	108†
12	14,200	12	1	66	6	15	2,030
13	10,000	9.5	3	79.5	1.5	6.5	650
14	9,400	15	2	79	0	4	776
20	17,400	27	1	70	0	2	348
24	11,000	43	1	55	0	1	110†
25	16,400	28.5	2.5	53.5	1	14.5	2,378
26	13,400	20	1	75	0	4	536
27	22,400	32	4	63	0	1	224
28	14,800	36	0	62	2	0	000
29	25,000	11	2	87	0	0	00
July 2	24,400	10	3	86	0	1	224
6	23,600	31	0	65	0	4	944
8	24,200	20	1	76	0	3	726
10	20,000	42	1	56	0	1	200
12	25,200	10	1	88	0	1	252
15	15,000	26	1	73	0	0	00
18	13,000	19	0	81	0	0	00
20	11,600	49	1	44	0	6	696
22	20,600	16	5	78	0	1	206§
23	16,800	14	2	82	0	2	336

*Weight 320 gm. †Two c.c. extract intraperitoneally. ‡Four c.c. extract intraperitoneally. Dyspnea, cyanosis, twitching, paralysis. §Weight 650 gm.

TABLE 5.—BLOOD-COUNT IN GUINEA-PIG 50. WEIGHT 245 GRAMS

Date ..... Sept. 2.	No. Leuko-cytes	Per Cent. Polynu-clears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Baso-phils	Per Cent. Eosin-ophils	No. of Eosin-ophils
Sept. 23	6,200	38	2	58	1	1	62*
27	4,600	47.5	5.5	47	0	0	00
30	7,600	50	7	39.5	2.5	1	76
Oct. 2	6,200	30.5	4.5	61.5	1.5	3	186
4	5,600	36	5.5	56	0	2.5	140
30	5,600	24	1	67	2	6	336†

*Two c.cm. extract intraperitoneally.

†Two c.c. solution in 0.5 per cent. salt solution of protein of *Ascaris* extract precipitated by acetone. Dyspnea, paralysis, death after 45 minutes.

TABLE 6.—BLOOD-COUNT IN GUINEA-PIG 47

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
June 26	14,600	42	0.5	54.5	0	3	438
27	12,000	32.5	3	62	1.5	1	120
28	8,000	32	2	63	0	3	240
29	11,000	19	1	79	0	1	110
July 5	9,600	34.5	2.5	63	0	0	000*
6	14,000	28	1.5	70	1.5	1	140
8	10,600	18	1	80	0	1	106
10	10,200	25.5	1.5	71.5	0	1.5	153*
11	18,400	55.5	1	40.5	0	3	552
12	25,400	24	2	70	1	3	762
13	14,200	28.5	0.5	67	0	4	562
15	11,600	32	3	64	0	1	116
18	11,800	6.5	1.5	91.5	0.5	0	000*
19	17,800	20	0	71	3	6	1,068
20	15,800	42	0.5	44	2	11.5	1,817
22	11,600	4	2	93	1	0	000
24	12,600	21	1	72	2	4	504*
25	24,400	35.5	0.5	53	4	7	1,708
26	19,600	32.5	2	50.5	2	13	2,548
27	23,600	18	1	75	1	5	1,180
29	8,400	51.5	0.5	40	7.5	0.5	42

*Two c.c. original extract intraperitoneally.

TABLE 7.—BLOOD-COUNTS IN GUINEA-PIG 36

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
May 8	16,000	46	4	40	2	8	1,280
20	11,200	44	5	40	1	10	1,120*
21	13,600	46	3	40	1	10	1,360*
22	18,400	20	5	73	0	2	268†
24	16,200	30	1	60	1	8	1,296†
27	7,000	21	4	68	1	6	420†
28	10,600	....	....	....	....	....	.....
31	9,000	39	2	49	2	8	720†
June 1	10,000	31	3	59	2	15	1,500†
3	15,000	19	6	59	1	15	2,250†
4	12,000	19	1	70	1	9	1,080†
5	18,000	28	3	58	1	10	1,800†
6	.....	....	....	....	....	....	.....†
7	7,800	27	1	60	0	12	936†
8	10,400	21	1	69	1.5	7.5	780†
10	13,400	22	0	68	1	9	1,200†
11	.....	....	....	....	....	....	.....†
13	.....	....	....	....	....	....	.....†
14	10,000	10	1	80	0	9	900
20	10,200	24	2	56	0	18	1,836
24	15,000	19	5	63	2	11	2,650
25	14,400	37	3	49	2	9	1,296
July 2	26,000	15	2	79	2	2	520
5	27,800	18	1	75	0	6	1,668

TABLE 7.—Continued

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
8	23,700	21	0	74	0	5	1,185
10	24,200	24	2	65	0	9	2,178
12	27,800	27	0	60	0	13	3,618
15	25,000	37	1	56	1	5	1,250†
16	31,600	46	0	43	1	10	3,160
17	22,800	28	1	65	0	6	1,368
18	32,800	23	1	69	1	6	1,968
20	28,600	24	0	62	1	13	3,618
22	23,600	33	0	44	1	22	5,172
23	22,000	27	0	63	1	9	1,980
26	21,600	38	0	53	0	9	1,944
29	13,000	40.5	2.5	38	3	16	2,080
Sept. 23	15,000	28	3	54	0	15	2,250
27	9,800	32	3.5	45.5	1.5	17.5	1,715
Oct. 2	12,000	22	3	56	0	19	2,280
4	10,000	14	1	71.5	2.5	11	1,100
Nov. 6	13,800	30	3	43	2	22	3,036‡
7	11,000	22.5	0	54	2	21.5	2,365
8	12,800	27	4	44	2	23	2,944
9	15,600	15	5	60	2	18	2,808

*Five c.c. original extract intraperitoneally; †2 c.c.; ‡2 c.c. extract previously boiled.

TABLE 8.—BLOOD-COUNTS IN GUINEA-PIG 48

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
Sept. 23	8,400	42	1	55.5	1.5	00	00*
27	13,200	46.5	4	48.5	0	1	132
30	10,000	25	2	72.5	0.5	0	00†
Oct. 1	13,000	66	2.5	28	0	3.5	395
2	11,600	60.5	3.5	32	2	2	232
4	8,800	19	0	80	1	0	00
7	12,000	21.5	2	76	0	0.5	60
9	14,400	....	....	....	....	....	.....
30	8,500	37	4	57	1	1	85‡
31	8,000	19.5	8	64.5	4.5	3.5	280
Nov. 1	10,800	40	2	46.5	0.5	11	1,188
2	5,400	16	2	78	0	4	216
6	10,000	41.5	2.5	53	1	2	200†
7	16,400	40.5	4	34.5	3	18	2,952
8	11,200	30	2	67	0	1	112
9	13,400	25	10	59.5	1	4.5	603
11	11,000	27.5	7.5	61.5	0.5	3	330§
12	11,000	32	4.5	63	0	0.5	55
13	7,200	13	4	83	0	00	00
14	8,600	21	1	75	2	1	86

*Two c.c. extract intraperitoneally.

†Two c.c. extract intraperitoneally (solution previously boiled).

‡One and five-tenths c.c. solution of acetone precipitate injected intraperitoneally.

§Two c.c. filtrate after coagulation of albumin of extract by heat and acidulation.

TABLE 9.—BLOOD-COUNTS IN GUINEA-PIG 53

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
Dec. 6	18,200	36	2	54	0	8	1,456*
7	21,000	72.5	6.5	14	1	6	1,260
11	22,800	36	7	45.5	3.5	8	1,824
13	20,000	50	11.5	35.5	0.5	2.5	500
16	10,200	27	7	60	0	6	612†
17	30,000	66	11	14	1	8	2,400*
18	11,800	43	4	40	1	12	1,416*
19	4,800	34.5	6.5	56.5	0.5	2	96*
20	9,400	30	4	57	2	7	658

*Two c.c. extract intraperitoneally; †3 c.c. extract intraperitoneally; dyspnea, tremor, convulsive movements.

TABLE 10.—BLOOD-COUNTS IN GUINEA-PIG 34

Date	No. Leukocytes	Per Cent. Polynuclears	Per Cent. Large Lymph.	Per Cent. Small Lymph.	Per Cent. Basophils	Per Cent. Eosinophils	No. of Eosinophils
May 8, 19, 15	10,000	23.5	3	70.5	1.5	1.5	150*
June 3	10,200	8	0	88	0	4	408†
3 p. m.	9,000	13	1.5	82.5	0	3	270
4:30 p. m.	14,000	44	1	48	1	5	700
June 4 2 p. m.	19,600	44	1	44.5	3.5	7	1,384
4 p. m.	14,000	39	3	46	1	10	1,400
June 5	17,000	15.5	2	78	0.5	5	850
6	8,000	17	0	60	0	23	1,840
7	12,000	4.5	4	82	0	9.5	1,140
8	12,200	19	0.5	76.5	0	4	488
10	17,600	38	2	57	0	3	428*
11	21,000	37.5	2.5	51.5	0.5	8	1,680
12	19,800	27	4	53	0	16	3,168
13	14,400	7.5	1	86.5	0	4	576
14	12,000	20	2	65	1	10	1,200
20	16,000	20	0.5	77.5	0	2	320
24	16,800	24	1	68	0	3	504*
25	28,000	23	1.5	67	0.5	10	2,800
26	13,400	33.5	0	45	2	19.5	2,613
27	12,000	4	1	91	1	3	360
28	12,600	4	3	89.5	0.5	3	378
29	12,400	25	1	67	0	6	744
July 2	12,000	2.5	0	92.5	1	4	480
3	17,000	37	1.5	50	1	9.5	1,615
5	13,000	24	1	74	0	1	130
8	8,400	24.5	1	68.5	1	5	420
10	14,200	29	2	62	2	5	710
12	9,600	2	1	96	1	1	96
15	9,000	33	0	59.5	0	7.5	675*
16	18,200	18	0.5	76.5	1	4	728
17	15,200	33	1	45	0	21	3,192
18	19,600	20	2.5	69.5	0	8	1,568
20	15,400	35	2	57	0	6	924
24	13,000	21.5	1	71	1.5	5	650
27	17,000	23	1	68	1	7	1,190*
29	13,600	32	3	49	1	15	2,040

*Two c.c. extract intraperitoneally. †Two c.c. extract intraperitoneally 2 p. m.

UNSATURATED FATTY ACID AS A NEUROLYTIC AGENT *

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This communication is a brief report of some experiments conducted with the purpose of determining whether certain hemolytic substances had a lytic effect on the nerve cell and what the consequences of this lytic action might be in the surrounding tissue. Experiments were conducted on five cats. The substances employed were oleic acid and triolein. Oleic acid, as is well known, is hemolytic, whereas triolein is not. Oleic acid is an unsaturated fatty acid, and on that account, as Faust and Tallquist[1] have shown, is hemolytic. It is capable of forming soaps with bases, and therefore of going into colloidal solution in the body fluids. Triolein is a combination of three molecules of oleic acid attached to a molecule of glycerin. It is a neutral fat; that is, it is not capable of forming soaps with bases and therefore can not go into colloidal solution in the body fluids. Triolein may, under suitable conditions, be emulsified in watery solutions. The difference in hemolytic action is, therefore, dependent on physical causes. The triolein, which contains three molecules of unsaturated fatty acid, does not hemolyze the red cell because it can not reach it, being present as an oil, however finely divided, and therefore unable, probably, to pass through the wall of the red cell. Oleic acid being able to go into colloidal solution is able to pass through the wall of the red blood-cell and mix colloidally with the contents.

In two cats oleic acid was injected into the brain; in three, triolein was injected under similar conditions into the brain.

PROTOCOLS

The protocols in brief are as follows:

Cat 98.—Jan. 31, 1912. The cat was etherized at 9:50 a. m., shaved, and the operation started at 10:30. An incision was made a little to the right of the median line about 1.5 cm. in length. The skull was trephined in about the center of this incision and 0.1 c.c. of oleic acid was injected. The wound was closed with two black silk sutures, dried with ether, and covered with collodion and cotton.

Feb. 3, 1912. The cat seemed to have recovered from the effects of the operation and was put in with the other cats.

Feb. 6, 1912. The sutures were removed and an attempt was made to reenter the brain with a needle. In doing this, the wound was opened. 0.3 c.c. of oleic acid was injected in all, 0.1 c.c. in each of three places. The last injection went the deepest, downward and backward. The etherization was begun at 3:05 p. m.

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* Submitted for publication in THE ARCHIVES Dec. 6, 1912.

† From the Laboratory of the Danvers State Hospital. No. 24 of the Danvers State Hospital Series.

1. Faust and Tallquist: Arch. f. exper. Path. u. Pharm., 1907, lvii, 375.

and the operation completed at 4:15 p. m. The wound was again closed with one silk suture, dried, and covered with collodion and cotton. The cat was found dead the next morning. The skull was opened and the brain removed. There was a hemorrhage at the site of the injection.

Autopsy.—The findings at autopsy were as follows: The gross section of the brain showed a large hemorrhagic focus in the white substance. The individual injections could be made out. The lesion had a chocolate brown color, which is characteristic of the combination of oleic acid and blood. It is noteworthy that the discoloration was not confined entirely to the site of the hemorrhage, but extended throughout the white matter in the neighborhood, so that on the affected side the gray matter appeared pale by contrast, the reverse of normal as shown

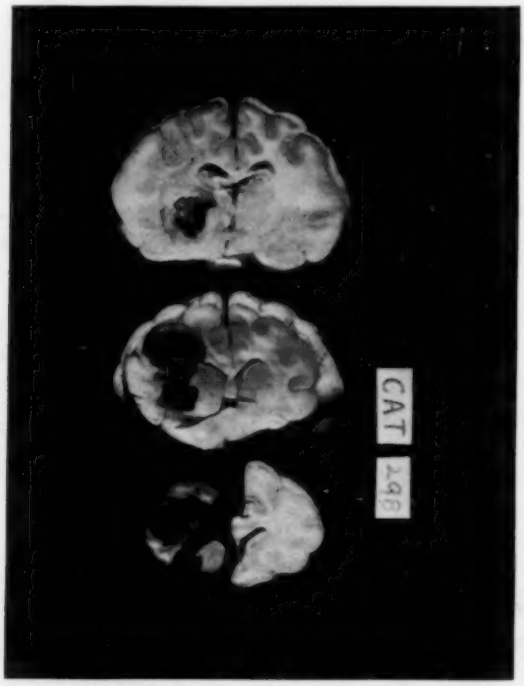

Fig. 1.—Brain of Cat 98. Four injections of 0.1 c.c. oleic acid each in about the same place into right hemisphere. Extensive hemorrhage. The right hemisphere is pushed over towards the left in the region of the median fissure. Convolutions show no flattening.

on the left side. The anterior portion of the hemorrhage represented the older of the injections (about a week between the injections). There were no signs of intracranial pressure at autopsy, yet the right hemisphere was distinctly enlarged by the injection, as might be seen in the cross section by the bulging of the median fissure.

Microscopical Examination.—Microscopically the hemorrhage itself showed a marked destruction of red blood-cells. The resulting brown pigment and detritus that filled the area of the lesion could account for the macroscopic dark color. In the neighborhood of the lesion this pigment and detritus was scattered thinly

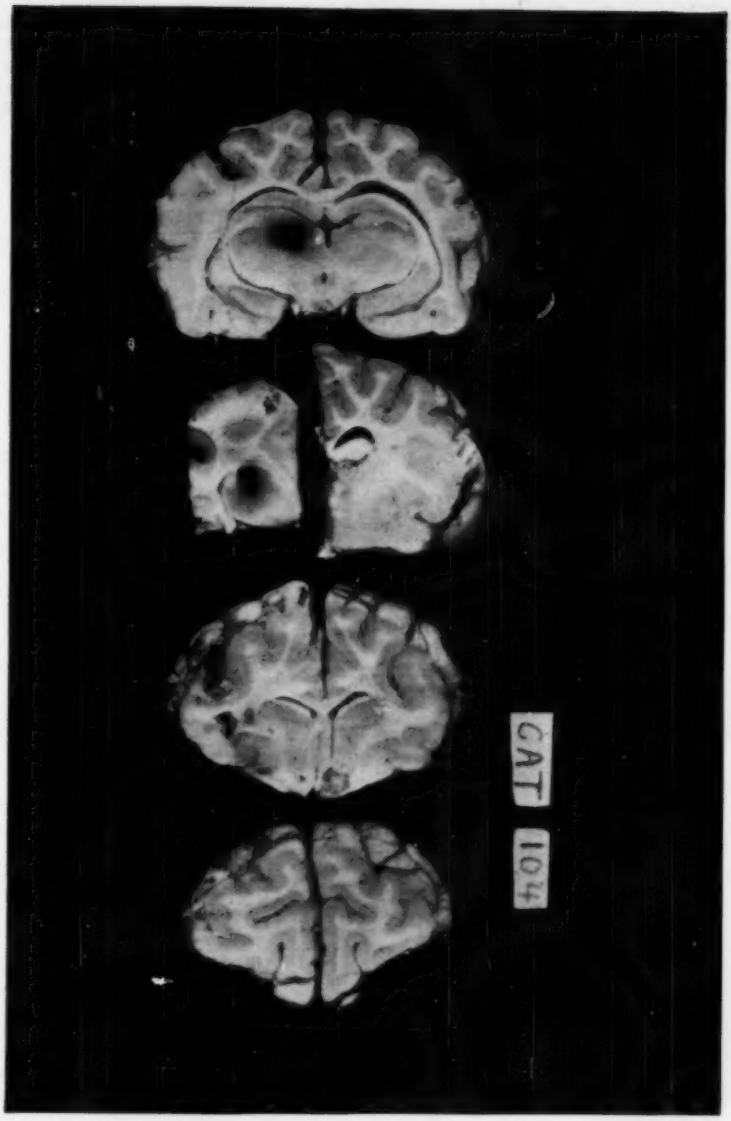

Fig. 2.—Brain of Cat 104. Two injections of 0.1 c.c. oleic acid at two different points within the right hemisphere. Distinct focal hemorrhages. Apparently no great displacement of tissue.

between the cells. The nerve cells had not taken up any. Here and there the nerve cells, however, were filled with globules of varying size that stained intensely with Scharlach R. There was here and there about the periphery of the lesion an amorphous hyaline substance staining a pale blue with hematoxylin and thionin, probably a calcium soap. There was a marked destruction of nerve cells and neuroglia, the nerve cells showing various stages of degeneration (vacuolization, etc.). Some nerve cells showed distinct satellitosis. There was a marked increase of perivascular cells. The endothelial cells about the vessels appeared to be filled with the brown pigment and granules taking the Sharlach R. rather indistinctly. The neuroglia at the membrana limitans of the brain tissue had become more active. The connective tissue cells around the blood vessels had large vesicular nuclei and might possibly be active. All along the course of the blood-vessels were cells with involuted nuclei that might be lymphocytes. The vessels were filled with fat. The increase of cells about the vessels was comparable to the increase of neuroglia cells.

Cat 104.—Feb. 27, 1912. Etherization was begun at 9:10 a. m. and completed at 9:30 a. m. An incision about 1.5 cm. was made just to the right of the median line and the skull was trephined. One tenth c.c. of oleic acid was injected in each of two places. The wound was closed with silk sutures and covered with collodion and cotton. The operation was completed at 10:10 a. m. The cat did not recover fully from the ether and died in the early part of the afternoon. On removing the calvarium the dura was found to be torn, apparently by the trephine. There was a hemorrhage over the point of injection extending over the side of the brain to the inferior surface. There was a brownish deposit of oil in the dura under the brain.

Microscopical Examination.—The duration of this experiment was only a few hours. The destruction of the blood-cells at the site of the main lesion was not as complete as in the previous experiment, but was nevertheless very marked. In the neighborhood of the lesion there was a large amount of detritus and blood-pigment in the brain substance. The reaction around the vessels observed in the foregoing experiment was not noticeable here, although here and there there was an indication of a beginning proliferation. In the immediate neighborhood of the lesion some of the nerve cells showed destruction. There was a marked satellitosis about these cells which was not noticeable at a distance from the lesion.

Cat 103.—Feb. 27, 1912. Etherization was begun at 10:05 a. m., and completed at 10:40 a. m. The incision was made just to the right of the median line and the skull was trephined. There was considerable hemorrhage of apparently venous blood. This was finally checked and 0.2 c.c. of triolein was injected in one place. The wound was closed with two black silk sutures, dried, and covered with collodion and cotton. The operation was completed at 11:25 a. m. Later in the afternoon the cat was rather stupid and in a semiconscious condition.

Feb. 28, 1912. The cat was found dead in the morning. The skull was opened and the brain removed. There was a hemorrhage beneath the dura at the point of injection. There was also a hemorrhage in the right lateral ventricle.

Cat 105.—Feb. 29, 1912. Etherized at 9:10 a. m. Operation begun at 9:55 a. m. The skull was trephined in about the same place as in the other cases, and 0.1 c.c. of triolein was injected. The wound was closed with silk suture, dried, and covered with collodion and cotton. The operation was completed at 10:10 a. m. The cat recovered from the ether very easily and seemed perfectly normal.

March 1, 1912. The cat was well and quite playful.

March 2, 1912. The cat was chloroformed and the skull opened and the brain removed. There was a slight hemorrhage beneath the dura at the point of injection.

Cat 106.—Feb. 29, 1912. The cat was etherized at 10:20 a. m. The operation was begun at 10:35 a. m. The skull was trephined on the right side and there was considerable bone hemorrhage. This was finally checked and 0.3 c.c. of triolein

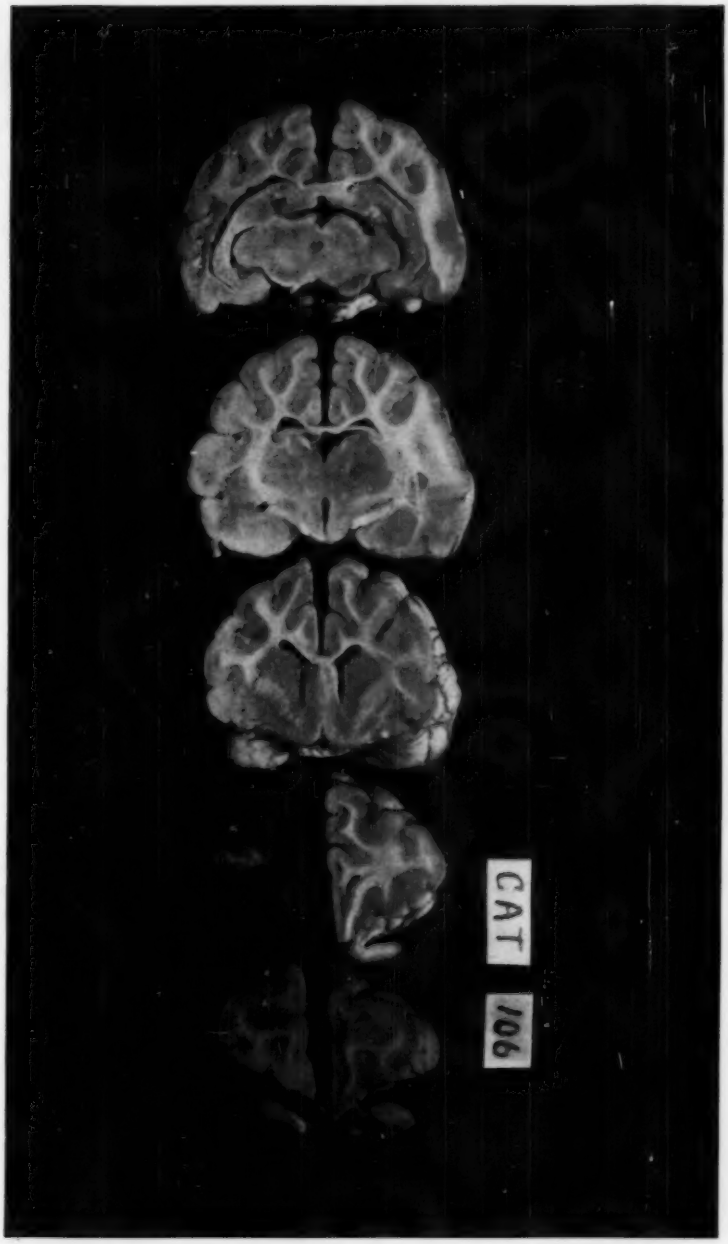

Fig. 3.—Brain of Cat 106. This picture shows the appearance of the brains of the three cats injected with triolein instead of oleic acid. 0.3 c.c. of triolein was injected into one place in the right hemisphere. Two days later the brain was removed. No hemorrhage. No sign of the injected oil, except microscopically.

was injected in one place in the right hemisphere. The wound was closed with three silk sutures, dried, and covered with collodion and cotton. The cat recovered from the effects of the ether and seemed normal.

March 1, 1912. The cat was well, and willing to be petted and to play with a straw.

March 2, 1912. The cat was chloroformed, the skull opened, and the brain removed. There was little to see externally except a slight congestion at the point of injection.

Microscopical Examination of the Brains of Cats 103, 105, 106.—With the exception of Cat 103 there were no signs of hemorrhage in these three cats. In 103 the hemorrhage was probably caused by a dull trephine rather than by the injection, as venous blood poured out from under the dura during the operation. The hemorrhage was confined to the subdural space and the lateral ventricle. The reactions, such as perivascular proliferation, nerve cell alteration, satellitosis, and the appearance of the brown detritus due to the destruction of the blood-cells, were either mild or in the latter case absent. Cat 103, which had a hemorrhage, showed microscopically practically no hemolysis. At the site of the hemorrhage there was a large amount of unabsorbed fat, apparently unaltered triolein. There was considerable unaltered triolein in the meshes of the pia mater. The pia cells appeared quite active. Cat 105 showed microscopically a small hemorrhage into the white substance. This hemorrhage in Cat 105 as in Cat 103 is to be regarded as mechanical in origin, as evidenced by its small size and by the absence of hemolysis and blood-pigment and detritus in its vicinity. The endothelial cells about these hemorrhages had taken up what fat they could, but there seemed to be no evidence of increase in the number of endothelial cells.

The reaction, therefore, seems in the case of triolein injections to be confined to the site of the injection and to the immediate disposal of as much triolein as possible, whereas in the case of oleic acid the size of the intracerebral hemorrhage, the nerve cell alteration, such as vacuolization, satellitosis, perivascular reaction and the appearance of the brown granular pigment, indicate a more or less destructive action on the nerve cells as well as on the red blood-cells. The perivascular proliferation and the satellitosis might, in view of these experiments, be regarded as of a protective nature, having possibly to do either with the neutralization of the unsaturated fatty acid or with the handling of the products of the destruction of the nerve cells (satellitosis).

SUMMARY

1. The above experiments show that unsaturated fatty acid, of which oleic acid is the type, is a neurolytic agent.

2. It is probable that this neurolytic action depends on the same properties as the hemolytic action of these substances.

3. Perivascular proliferation and satellitosis may be associated with pathological processes in which lytic fatty substances play an important part.

4. An intracerebral hemorrhage may be produced experimentally without altering the blood-pressure and without trauma, but by means of chemical action alone.

5. A method is hereby given for producing hemorrhages within the nervous system at any desired point.

74 Fenwood Road.

A CRITICAL STUDY OF A CASE OF MYIASIS DUE TO *ERISTALIS* *

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Sept. 2, 1912, one of us (Muir) was called in to see a boy, J. H., 5 years old, who had been ailing for about ten weeks and who was under medical treatment for indigestion and obstinate constipation for about five weeks of that time. The child was emaciated and anemic. Very striking symptoms were the constant and pronounced twitching of the eyelids and other nervous movements. He gritted his teeth in his sleep at times, and made convulsive movements of the limbs. When awake he complained of pain in the limbs and of headache. The emaciation seemed to be due to the fact that the boy had for some time vomited almost everything he ate. The breath was very bad, "worse than rotten eggs," according to his parents.

On the basis of the nervous and digestive disturbance and the general debility, a diagnosis of worm infestation was made. The mother was told to call and get some medicine, but instead of doing so she bought a bottle of a proprietary worm remedy, on the advice of a neighbor, and gave the child a dose, according to the directions, at noon of September 3. The stool was passed at evening into the slop jar which was in regular use. The jar had been rinsed with city water from the hydrant in the morning and allowed to dry during the day. There is no water on the place except that of the Colorado Springs water system, available at a hydrant in the yard and a sink tap in the house. On looking at the stool immediately after its passage, the boy noticed a strange object moving around in it and called the father and mother to see it. They found the object wriggling around vigorously in the feces and urine, and attempting at times to climb up the sides of the jar. The specimen was removed and put in water, in which it thrashed around for a time, and was then put in alcohol, in which it shriveled considerably, according to the mother and father. The specimen was turned over to Muir, who referred it to Dr. Trossbach of Colorado Springs. It was sent by him to Mr. W. W. Cort of Colorado College, who referred it to Hall, then in Colorado Springs on government field work, for identification.

The specimen is one of the "rat-tailed larvae," a larva of one of the family *Syrphidae* of the order *Diptera* or flies. The mother states that

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the larva was originally yellowish with three brown stripes, but when it came into our hands it was black over the entire body except for a little brownish coloring on the "tail." The anterior part, or body proper, is 1.55 cm. long, while the "tail" is 1.65 cm. long, a total length of 3.2 cm. This "tail" is really the breathing tube of the animal. These larvae live in soft mud, wet manure, privies and other places where there is plenty of sufficiently moist food, and the "tail" is a stigmatic tube which is held projected upward at the angle necessary to keep the tip above the wet material in which the larva lives, thereby enabling it to bring down a supply of air for breathing.

Williston (1886), in his synopsis of the North American *Syrphidae*, describes the larvae as follows:

> The larvae are usually not very elongate, with firm, sometimes tough skin, the head segments small and extensile. Like the other families of the *Cyclorrapha*, the larvae of *Syrphidae* do not have a distinctly differentiated head. The external mouth-parts are either wholly wanting, with only a soft fleshy opening, or there are two or four outwardly directed hooklets. There are also short, small, one- or two-jointed fleshy antennae. The body is smooth or provided with soft, conical projections and bristles: below usually with seven pairs of abdominal feet. At the posterior end, the body terminates in a more or less elongate tube, single or double—the stigmata. This sometimes forms a short, almost chitinized, tubercular projection on the dorsal part of the last segment; at other times it is very long, longer than the body, slender, composed of two joints, the one sliding within the other, like the joints of a telescope. It is never divaricate, or forked at the tip, as in many of the other tailed larvae in the allied families.

Supposed cases of gastric or intestinal myiasis should always be given very careful consideration and investigation. Our actual knowledge of the subject is limited. To what extent various dipterous larvae, commonly occurring as free-living forms, can survive the digestive processes of the alimentary canal and pass out in the feces undigested and even alive and uninjured, is something of which we have too little information. How long such larvae could persist in the alimentary canal, deriving their nourishment from the digested food of the host, and their air supply from the ingested atmospheric air, can not yet be said. We may surmise, and plenty of surmising has been done, but the fine field for experimental investigation which the subject affords is untouched except for such few records as those of Alessandrini (1909), who has fed the cheese skipper, *Piophila casei*, to dogs, and finds that it passes through the digestive tract alive and uninjured, causing intestinal lesions in the dog. Even the information which would be furnished by the publication of carefully investigated cases is, to a large extent, lacking. Banks (1912) quotes Walsh as follows:

> Taking everything into consideration, we doubt whether, out of ten thousand cases where the larvae of two-winged flies have existed in considerable numbers in the human intestines, more than one single case has been recorded in print for the edification of the world by competent entomological authority.

In addition to our lack of adequate knowledge of the possibility of facultative parasitism on the part of various fly larvae, there is the certainty of error in some cases, due to deliberate fraud on the part of hysterical patients or to accidental contamination of the stool. So many things are sent to specialists for identification as parasites, which prove to be free-living forms incapable of parasitic modes of life, that anything other than an obligate parasite demands a careful investigation. When a farmer states that he defecated in or near the stable and found worms in the stool, and the worms prove to be "rat-tailed larvae," it is much more likely that the larvae were already in the manure at the place of defecation than that they were actually passed. And even when such larvae are found in the slop jar where the jar has been rinsed with water from an open spring, the possibility of the larvae having been in the spring and having remained in the jar after rinsing must bring the find under suspicion.

Dr. Albert Hassall of the Bureau of Animal Industry has related to one of us (Hall) an instance which indicates the need of care in passing on cases of myiasis. He states that on one occasion he saw a slop jar, kept in a privy during the day and only brought in for use at night, with a larva of *Eristalis* hanging over it, just ready to drop, while it was in the privy. Had the larva fallen unobserved and been found at the appropriate time, it would have been ample evidence to most persons that it had been passed into the jar by the persons using it.

Of myiasis in general, Banks (1912) says:

> There is a considerable number of flies whose larvae either regularly or occasionally live in substances used by man as food. The great majority pass through the intestinal tract without our knowledge, for most of them cause little or no trouble. But sometimes with patients in hospitals or asylums, or in private practice, the physician discovers these maggots, and often suspects them of causing the malady or weakness of his patient.
>
> Many such specimens have been sent to entomologists, but owing to the fact that no one had studied these forms, their characters were little understood, and the identifications have not been of much value. Most of these larvae belong to a few closely related families of flies that were formerly covered by the name *Muscidae*. The arrangement of the flies has been the subject of much diverse opinion, while the knowledge of the larvae is very fragmentary.
>
> When we consider that these dipterous larvae occur in decaying fruits and vegetables and on fresh and cooked meats; that the blow-fly, for example, will deposit on meats in a pantry; that other maggots occur in cheese, oleomargarin, etc., and that pies and puddings in restaurants are accessible and suitable to them, it can readily be seen that a great number of these maggots must be swallowed by persons each year, and mostly without any serious consequences. Besides these there are the fruit-flies, whose larvae live in apples, cherries, gooseberries and oranges; and the pomace-flies that hover around grapes, pears, and other fruits.

So far as we have been able to locate it, the literature relating to the subject of myiasis due to larvae of the *Syrphidae*, is as follows:

Odhelius (1789) records a case from Carlstad, Sweden, in which fly larvae, determined as those of *Musca pendula*, were claimed by Dr.

Flanck of that place to have been passed by a 17-year-old girl patient. The patient had been in good health until three years previous, and then became sickly, complaining of severe pain in the stomach, of giddiness and headache, inflammation of the throat, and such great weakness that she was often compelled to go to bed. In the summer of 1787 she had to have medical treatment. At that time mineral waters were prescribed, jalap, aloes and calomel were administered, and as a result these larvae were dislodged and the patient returned to her former health after some weeks. The patient's diet previous to the time she became sick consisted largely of milk, and included occasionally sour curdled milk from the country. She was very fond of cheese rind or the outer part of cheese. Odhelius suspects that the patient became infested by ingesting eggs laid by the fly either in the cream on the sour milk or on the surface of the cheese.

Joseph (1887) notes this case and parenthetically notes that the larvae were probably *Homolomyia canicularis*, but since Odhelius specifies them as rat-tailed larvae there seems to be little warrant for Joseph's assumption. It seems probable that this is the case referred to by Gilbert (1908) as a record of *Eristalis pendulus*, by Brumpt (1910) as one of *Helophilus pendulinus*, and by Gedoelst (1911) as one of *Tubifera pendula*. It appears from Coquillet (1910) that the correct name is *Helophilus pendulus*, the type species of *Helophilus* being *Musca pendula*. According to the same authority, *Eristalis*, type *Musca tenax*, is merely a synonym of *Tubifera*, but in a paper of this sort we have thought it better to adhere to the commoner and more generally used name.

Wagner (1870) records a case of infestation with *E. arbustorum*. One of four to six specimens was sent to him by Dr. Kind and the adult fly was bred and determined by him. The larvae were passed, following a dose of rhubarb, by a woman who imagined she had worms. Dr. Kind had carefully examined the feces of the patient every day since the beginning of March, the larvae being passed on March 10, and had also made such careful examination of the other circumstances in the case as to leave no doubt as to the origin of the larvae. The circumstance which makes the finding especially plausible is that only an occasional pupa, and never a larva, survives the winter. The previous winter had been very severe and he surmises that it would require some explaining to clear up the question as to where this larva had come from at the beginning of March if this was not a good case of myiasis. Wagner points out that the conditions in the digestive tract simulate closely the ones in which the larva lives in Nature; that there is plenty of air, warmth and food, and even such mephitic gases as those with which the larva is usually surrounded. He is of the opinion that probably the larvae were located

in the stomach after the habit of *Gastrophilus,* rather than in the intestine. He notes that he has not infrequently found rain water draining from compost heaps into inadequately protected springs, and considers it very probable that *Eristalis* eggs from compost heaps and the like would be ingested in drinking water.

Brumpt (1910) has erroneously referred this case to Joseph (1887). Joseph merely quotes Wagner's case.

Leidy (1874) has the following note:

> Prof. Leidy * * * remarked that Dr. Keyser, of this city [Philadelphia], the evening previously had brought to him for examination a worm, which was stated to have been removed from the cavity of the nose of a patient. He recognized the worm as a rat-tailed larva apparently of the genus *Eristalis,* and inquired of those members interested in entomology, if they had ever known this insect to be found as a parasite in the human body. Both Drs. Le Conte and Horn said that they had never heard of this genus being parasitic.

Riley (1890) notes "the sending of *Eristalis dimidiatus* in the larva state by Dr. J. W. Compton, of Evansville, Ind., who stated that they were passed from the bowels of a young woman," and "the recent sending of larvae of *Eristalis tenax* by Dr. J. A. Lintner, to whom they had been sent as having been found under similar circumstances."

Riley and Howard (1890) quote the following from a letter from Dr. Frontis, of Johnston, S. C.:

> I send by mail to-day a specimen of a small worm that infests a well at this place. Ordinary cleaning of the well does not get rid of them, but they are quickly redeveloped, so that one bucket of water will frequently contain three or four. As a matter of course the water is not used for drinking purposes, but the proprietor would like to use it and be freed from these pests.

A similar case is noted in the files of the U. S. Bureau of Entomology of specimens received from Lime Rock, R. I., in December, 1894, with a report that there were millions, apparently all dead, in a well.

The "worms" in both cases were determined as *Eristalis,* probably *E. tenax.* This, of course, indicates at once one source of human infestation.

Shattock (1908) has an observation on the larvae of *Eristalis tenax,* three specimens of which were sent in from Totten, Hants (England), with the statement that twenty or thirty had been passed at one time and some others singly after a few days' interval. "Full doses of santonin, and of mercury, and other intestinal antiseptics had been given." The collector, Mr. H. McQuade, writes: "There is not the smallest doubt but the specimens were passed by the bowel; the whole length of time they were observed was about four weeks, and none have been seen since those which I sent were passed." The patient had recently arrived from France, where she had eaten a good deal of watercress. In comment, Shattock says:

In the present case the ova were most probably taken by the patient concealed in watercress, and subsequently underwent development into larvae in the intestinal canal. When it is remembered that sewers constitute one of the habitats of the larvae there is nothing surprising in the presence of the latter in the contents of the intestine. The oxygen for respiration during their development would be furnished, one must believe, by the air naturally swallowed.

McCampbell and Corper (1909) report a mixed infection with *Musca domestica, Anthomyia canicularis* and *Eristalis tenax,* and say of the last-named: "Cases of myiasis with *Eristalis tenax* larvae are extremely rare. No cases are recorded in which accurate data are given. It is the rarest of the three species considered in this report." Their critical study of their case is not convincing and such hypothetical explanations of the abundance of larvae as due to the reproduction of the larvae within the intestine, or the development of the adult fly and subsequent oviposition in the intestine, are quite at variance with known facts. They state that cathartics and aperients have failed to eliminate the larvae. In this connection it may be noted that in our case an anthelmintic seems to have been satisfactory.

From the general statements of Brumpt (1910) and Gedoelst (1911) one would infer that the larvae of *Eristalis dimidiatus* and of *Helophilus pendulus* have been observed in several cases, but we are unable to locate any published records other than those given here.

Gilbert (1908) says of the *Syrphidae*:

But few cases are recorded of infection by larvae of this family and these all by larvae of the genus *Eristalis*, which are found in decaying vegetables and fruits, and in decaying organic matter of all kinds, or in water saturated with organic remains. The following species are reported to have been passed from the bowels, but no definite history of the manner of infection or of the duration of their parasitic existence is given: *Eristalis dimidiatus, Eristalis tenax, Eristalis arbustorum, Eristalis pendulus.*

Banks (1912) says:

There are other flies whose larvae are sometimes reported as swallowed by persons, particularly the rat-tailed larvae of *Eristalis*, which sometimes gets into drinking water.

In the Bureau of Animal Industry collection of parasites there is a specimen of *Eristalis* larva collected in Portland, Me., in 1899, and said to have been passed by man. There is no further information in regard to the case. There are also eight *Eristalis* larvae sent in from Laurel, Md., in 1909, with the statement that they were passed in a jelly-like substance from the vagina of cattle. In correspondence relative to these specimens, Dr. B. H. Ransom suggests to the sender:

Probably a diseased condition of the organ in which you found these larvae created an odor which attracted the flies to this particular place with the result that they have deposited their young in the unusual location.

Through the courtesy of Dr. L. O. Howard and Mr. R. S. Clifton, of the U. S. Bureau of Entomology, we note the following records from the files of the bureau:

A larval specimen of *Eristalis sp.* was received from a physician in Adell, Wis., in September, 1910, with the report that it was passed by a patient.

A similar specimen was sent in from Syracuse, N. Y., in October, 1906, with a statement that it was supposed to have been vomited by a woman suffering from vomiting of pregnancy.

A larva of *Eristalis sp.* or *Helophilus sp.* was sent in from Bessemer, Ala., in October, 1905, with a statement that twenty-four of them had been passed by a colored child 19 months old after severe intestinal irritation.

Another larva of *Eristalis sp.* or *Helophilus sp.* was sent in from Pittsburgh in October, 1905, with the report that it was taken alive from the stool of a man who had just returned from a hunting trip and who had drunk stagnant water on the trip.

It appears to be customary to refer most cases of rat-tailed larvae to *Eristalis tenax.* An examination of the available entomological literature does not furnish us with an adequate description of the larvae of the various species of *Eristalis,* and in fact indicates that these, like many other of the *Diptera* larvae, are not well known. The very useful paper on diptera larvae by Banks (1912) unfortunately does not deal with the *Syrphidae.* The fact that *E. tenax* is very common and widely distributed is possibly the warrant for many of these identifications. For ourselves we are unable to identify our specimen closer than to say that it is a larva of *Eristalis,* and possibly of *E. tenax* for the reason given—that this is a common species.

The mother of the boy from whom our specimen was obtained states that a second larva was passed the morning after the first, but that it was dead, and as it was injured in getting it from the feces it was thrown away. Two days later a third specimen was passed and was kept. This was later turned over to us and proved to be a curd of some sort, a spurious parasite superficially resembling the first. It is possible that the second specimen, which was thrown away, was something similar.

Since the passage of the first larva the child has improved in health considerably and his appearance is now that of the normal healthy child. The nervous symptoms have disappeared and the persistent vomiting has ceased. Food is retained and digested, and the breath is no longer unpleasant.

The boy has lived in Colorado Springs for four years, so that the infestation, if genuine, must be referred to this place. He had been ailing for several weeks, becoming worse July 28, 1912. The previous evening he had eaten some peaches which his mother says were over-ripe. The day following the eating of the peaches the boy did not feel well and asked to be taken for a car ride to Stratton Park, an outlying city park. On the way out he vomited repeatedly, and as the vomiting continued

after they arrived at the park, they returned home. From that time the vomiting persisted, accompanied by an obstinate constipation and loss of weight, until the passage of the larva.

Not far from the house, perhaps 150 yards away, is an irrigation ditch which has running water in it part of the time and standing pools of water when the headgate is shut. Quite a little trash and refuse, including kitchen refuse, rotten vegetables, and even dead animals, are dumped in this ditch by careless persons. The boy and his companions play in this ditch and the boy says he has drunk of the water in the ditch. He also plays around a neighbor's stable and during the very rainy July of this year the stable manure would have afforded an excellent place for the breeding of rat-tailed larvae.

There are, then, three apparent chances for infection—the stable, the ditch and the over-ripe peaches. The onset of the vomiting following the eating of the peaches points to them as a possible source. "Overripe" is, of course, merely another word for decaying, and these larvae live in decaying vegetable matter among other things. The fact that the boy had been ailing before eating the peaches, suggests that the infestation antedates the eating of the peaches. The ditch is another likely source of infestation, as a larva breeding in the soft mud of the pools may have been ingested by the boy in water from the pools or in the muddy ditch water as the larva was swept along by the current. There is no obvious way in which the boy would get the larva from the stable except by eating it. While we do not think this likely, it is a possibility that must be kept in mind. Cases of children who have deliberately eaten insects and their larvae are by no means unknown.

As intimated earlier in this paper, there are three possibilities as to the truth or falsity of this case as one of myiasis. Either there was deliberate fraud on the part of the child or its parents, or the stool was contaminated, or the case is a genuine example of gastric or intestinal myiasis.

All the evidence is against the idea of fraud. The parents appear to be rational, sensible and respectable people. They are hard-working persons with no evidence of hysterical tendencies or nervous disorders. They had looked on the specimen as an intestinal worm and were inclined to be incredulous when told that it was a larva or maggot; they had never seen maggots with "tails" before and volunteered that they would look for them after this. They further exhibited an astonishment that was not simulated when told that other cases of the sort had been reported, so they were not imitating other cases. No attempt was made to advertise the find or to excite surprise or sympathy with it. They had looked on it as a banal case of "worms." We consider it out of the question that either of them should have deliberately put the larva in

the slop jar. The preservation of the third specimen, a spurious parasite, argues against the idea. At the time the boy defecated, the entire family was undressed ready for bed, a thing which eliminates the idea of the boy's deliberately contributing the specimen at that time. There is no reason to suspect the boy of such a thing, and no likelihood that a 5-year-old child could successfully, or would, carry around a large, violently wriggling larva for the purpose of fooling anyone in this way. It is extremely unlikely that he would do so during the afternoon and out of the question that he could do so when undressed and ready for bed.

The possibility of contamination of the stool, so far as we can see, is entirely a question of whether the larva was bred in or washed into the Colorado Springs water system, passed its screens, survived the pressure, entered the slop jar when it was washed and rinsed out in the morning, remained there all day, alive and unnoticed, after the jar dried, as it very quickly would in the dry air of Colorado Springs—the actual atmospheric humidity being low even on rainy days—and was then found after defecation. This seems very unlikely and even, in our opinion, out of the question. The water supply of Colorado Springs comes from deep alpine lakes, down a mountain stream, then through pipes to deep reservoirs on a high mesa, and then through pipes to the city. None of these would serve as breeding places for these larvae, and larvae which might wash into any of them—an unlikely thing of itself—would be drowned long before reaching the patient's residence. Moreover, to suppose that such an extremely rare thing as a rat-tailed larva in the city water system could perform the practically impossible feat of coming through that system alive and would show up at precisely the right time following the taking of a vermifuge at a particular residence, is to strain even the very common credulity which people manifest in regard to coincidences as explanations of unusual things.

While we have no such conclusive evidence as would be afforded by a case where the slop jar had actually been examined by a competent and skeptical person just before defecation, nevertheless, it seems more reasonable to regard this case as one of gastric or intestinal myiasis than as one of fraud or contamination. The child had three good possible sources of infection and, by his own admission, habits that could easily lead to infection. Carelessness in eating and drinking is more or less characteristic of children. Flies of the family *Syrphidae* are abundant around the streets of Colorado Springs, and the following adult flies were collected there or nearby by Hall and Mr. Horace Ragle, of Colorado Springs, during the summer of 1912 and determined by Mr. Frederick Knab, of the U. S. National Museum: *Eristalis tenax, E. hirtus, Syrphus sp.*, and *Eupeodes volucris*. The relief after the passage of the larva is additional evidence and there is no possibility that the child was malingering. Five-

year-old children could not and would not "fake" vomiting, restlessness in sleep, and loss of weight, or recover from these by suggestion, especially as the suggestion has not been emphasized by anyone.

We consider this as probably gastric rather than intestinal myiasis on account of the persistent and prompt vomiting after taking food, and regard this as due to irritation from the spiny-footed larva and its movements. It is likely that a large, active larva would succeed in evading the pylorus. Such related dipterous larvae as *Gastrophilus* live in the stomach as obligate parasites and carry on stigmatic breathing successfully. Most cases of myiasis are reported as intestinal rather than gastric when larvae are found in the feces, but this seems to be as much a matter of habit as of investigation and careful decision. *Pollenia rudis* is listed by Gedoelst (1911) as found in gastric myiasis. A larva supplied with the stigmatic apparatus of *Eristalis* would apparently be fitted for life in a stomach with a small amount of food and plenty of the atmospheric air which is swallowed in eating and drinking and at other times. Such a condition would simulate the normal life conditions fairly closely. That the stomach would not fill to the point where it would drown the larva might be insured by the vomiting, perhaps automatically, the activity of the larva increasing as the stomach filled to where it threatened to cover the rising stigmatic tubes, and so setting up an irritation leading to vomiting. The mother states that the child's stomach was extremely intolerant of milk and that drinking milk was promptly followed by vomiting. This suggests that milk, usually taken in long drinks and considerable quantities, quickly threatened the larva with drowning and set up such activity as promptly to cause vomiting.

In conclusion, it will be noted that the evidence in favor of this case as being an actual case of myiasis, while not conclusive, is nevertheless more nearly conclusive than that of any case involving the larvae of the *Syrphidae* which we have found recorded. A summary of the seven published cases known to us is as follows: Odhelius's case of *Helophilus pendulus;* Wagner's case of *Eristalis arbustorum;* Leidy's case of *Eristalis sp.* [nasal]; Riley's case of *Eristalis dimidiatus* and case of *E. tenax;* Shattock's case of *E. tenax;* and McCampbell and Corper's case of *E. tenax.* To this should be added the case recorded in this paper, the four cases from man recorded in the files of the Bureau of Entomology, and the one case from man and one from the cow [vaginal] recorded in the files of the Bureau of Animal Industry.

BIBLIOGRAPHY

Alessandrini, Giulio: Studi ed esperienze sulle larve della *Piophila casei.* (Vermi del formaggio) Arch. de parasitol., Par. 1909, xiii, 337.

Banks, Nathan: The Structure of Certain Dipterous Larvae with Particular Reference to Those in Human Food, Bull. 22 Tech. Ser., Bureau Entom., U. S. Dept. Agric., Jan. 10, 1912.

Brumpt, E.: Précis de parasitologie. With preface by R. Blanchard. 1910. Paris.

Coquillet, D. W.: The Type-Species of the North American Genera of Diptera. Washington, 1910. (Proc. U. S. Nat. Mus. (1719), xxxvii.)

Gedoelst, L.: Synopsis de parasitologie de l'homme et des animaux domestiques. Lierre & Bruxelles, 1911.

Gilbert, N. C.: Infection of Man by Dipterous Larvae. With Report of Four Cases. THE ARCHIVES INT. MED., 1908, ii, 226.

Joseph, Gustav: Ueber Fliegen als Schädlinge und Parasiten des Menschen. Deutsche Med. Ztg., Berl., 1887, viii, August 11, p. 713; August 15, p. 725.

Leidy, Joseph: *Eristalis* from Cavity of Nose. (Abstract of Remarks, Oct. 14.) Proc. Acad. Nat. Sc. Phila., 1874, xxv, 365.

McCampbell, E. F., and Corper, H. J.: Myiasis Intestinalis Due to Infection with Three Species of Dipterous Larvae. Jour. Am. Med. Assn., 1909, liii, 1160.

Odhelius, Joh. L.: Et sällsynt slags Larver, utdrifne ifrån et ungt Fruntimmer under en Brunscur. K. Vetensk. Acad. n. Handl., Stockholm, 1789, x, 221.

Riley, Charles Valentine: [Note on Dipterous Insects Passed from the Rectum of Man.] Secretary's abstract of note read before Entom. Soc. Wash., Dec. 5, 1889; Insect Life, Wash., 1890, ii, 261.

Riley, Charles Valentine, and Howard, L. O.: [*Eristalis* in Well Water.] Reply to query. Insect Life, Wash., 1890, iii, 22.

Shattock, Samuel G.: Three Specimens of the Larvae of *Eristalis tenax*, Passed by the Bowel. Proc. Roy. Soc. Med., Lond., Path. Sect., 1908, i, 147; ibid., Lancet, Lond., 1908, clxxiv, 934.

Wagner, B.: Die Made von *Eristalis arbustorum* L. als Parasit im menschlichen Darmkanale. Entom. Ztg., Stettin, 1870, xxxi, 78.

Williston, Samuel W.: Synopsis of the North American Syrphidae. Bull. 31, U. S. Nat. Mus., Wash., 1886.

THE INTERPRETATION OF THE NORMAL ELECTROCARDIOGRAM. A CRITICAL AND EXPERIMENTAL STUDY *

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INTRODUCTION

Waller,[1] in 1888, was the first to demonstrate that the action currents arising from the heart muscle during its contraction were conducted out to the peripheral tissues in sufficient strength to be detected by leading off from the limbs to an electrometer. It was not, however, until the improvement and adaptation to physiological work of the thread galvanometer by Einthoven,[2] in 1903, that any considerable interest in this matter was aroused. In the nine years since Einthoven's first publication, a very large and rapidly increasing literature on the subject of the electrocardiogram has appeared, and great interest has developed as a result of its evident clinical and physiological importance. Notwithstanding the great amount of work that has been done, the various workers in this field are by no means agreed as to the interpretation of the normal electrocardiogram, and as a result, the interpretation of those departures from the normal that occur in cardiac disease, as well as the significance of the normal electrocardiographic curve in reference to the normal course of the cardiac impulse over the heart, has been largely influenced by the point of view held by the individual investigator.

Up to the present time the usefulness of the electrocardiogram from the clinical standpoint has been principally evident in the analysis of two classes of abnormal cardiac conditions; first, the heart arhythmias, including under this the disturbances arising from depressed conductivity as well as those arising from ectopic impulse formation; and second, the condition and activity of the auricles (auricular hypertrophy, auricular fibrillation, etc.). In these two classes of conditions the electrocardiogram has only certain technical advantages over the venous and esophageal pulse tracings.

In a third group of cases however, of great importance clinically and to which in its present development at least the venous pulse is not applicable as a means of study, namely, the functional activity of the

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1. Waller: Philosoph. Tr. Royal Soc., 1888, 178B, 215.
2. Einthoven: Ann. der Physik., 1903, xii, 1059.

ventricles, the electrocardiogram has yielded results which are to a considerable degree interpreted differently by different investigators. This is mainly due, it would seem, to the marked differences in interpretation of that portion of the normal electrocardiogram which represents ventricular activity (the Q, R, S and T waves of Einthoven). It is the purpose of the present paper to present certain facts from the literature and certain experimental observations of our own, which, while bearing on the interpretation of the electrocardiogram as a whole, have particular reference to the ventricular portion.

HISTORICAL REVIEW

An attempt at a complete review of the development of the electrocardiogram and the immense amount of clinical and experimental work of this subject would be beyond the scope of this paper. Reference will be made only to articles which bear directly or indirectly on the interpretation of its features as applied to the course of the cardiac impulse and the contraction of the different parts of the heart. An extensive review of the literature up to 1910 is given in the monograph of Kraus and Nicolai.[3]

The normal electrocardiogram, as described by Einthoven,[4] shows always at least three waves, all usually in the same direction. If the leads to the galvanometer are so arranged that a movement upward of the thread on the record occurs with relative negativity of the electrode in contact with that portion of the body more directly connected with the base of the heart, all of these three waves are in the upward direction. The three waves, according to the nomenclature of Einthoven, are designated P, R and T. With certain leads, T may be directed downward, and this wave may change its direction independently of the other waves in apparently normal beating hearts. Aside from these waves, two downward-directed waves may occur. The first of these (the Q wave of Einthoven) immediately precedes the R. It is quite infrequent and is regarded by Kraus and Nicolai[3] as abnormal. The second downward wave (the S wave of Einthoven) follows at once on the R. It is present in the electrocardiograms from adults in about one-third of all cases. In electrocardiograms from children it is always present and its frequency and size decrease with age (Kraus and Nicolai[5]). Finally, there are two parts of the curve which are described as having a horizontal course indicating equal potential of base and apex of the heart, one between the P and Q (or R) waves, the other between the R (or S) and T waves.

3. Kraus and Nicolai: Das Elektrokardiogram des Gesunden und Kranken Menschen, Leipzig, 1910.

4. Einthoven: Arch. internat. de physiol., 1906, iv, 132; Arch. f. d. ges. Physiol., 1908, cxxii, 517.

5. Kraus and Nicolai: Berl. klin. Wchnschr., 1907, lxiv, 765 and 811.

In his first publication, Einthoven ascribed the P and Q waves to the contraction of the auricles, the R, S and T waves to ventricular systole. Later work by Einthoven and others has shown that only the P wave of the normal electrocardiogram can be ascribed to the auricle. The P wave is the only wave present when the auricle alone contracts (Einthoven, Kraus and Nicolai). It is enlarged in auricular hypertrophy and absent in the absence of auricular contraction. The work of Samojloff[6] and of Kraus and Nicolai[3] tend to show that the P wave of the electrocardiogram is the first part of a diphasic variation which is evident in its entirety when the leads to the galvanometer are from the exposed auricle and not from the surface of the body.

In the interpretation of the group of waves which precede or accompany the first part of ventricular systole (Q, R and S), the views which have had widest acceptance are those of Einthoven and of Kraus and Nicolai. According to Einthoven,[4] the horizontal portion of the electrocardiogram following the auricular wave (P) and lying between this wave and the first ventricular wave, represents the time necessary for the impulse to pass through the His bundle and its various ramifications, where physiological connection is made with the ventricular musculature. During this time the galvanometer shows no movement, because both auricles and ventricles are at rest and the contraction wave through the connecting bundle is so weak as to cause practically no difference in potential. Einthoven evidently regards the passage of the impulse through the bundle to be associated with a weak contraction.[7] The next movement of the galvanometer thread does not occur, therefore, until the impulse has reached the ventricular musculature. The extensive branchings and connections of the auriculo-ventricular bundle, as shown by the work of Tawara,[8] ensure that the excitation passing downward from the auricles reaches the ventricle, not merely at the base or apex, but over a large surface of ventricular musculature. With the passage of the excitation into the ventricle the complex Q R S occurs. If the impulse first reaches the portions of the ventricles lying toward the apex, the apex of the heart shows relative negativity to the base, and the downward directed Q wave occurs. If other portions of the ventricles lying nearer the base (particularly the right ventricular base) first receive the

6. Samojloff: Beitr. z. Physiol. u. Pathol., Festschr. f. Hermann, 1908, p. 171; Samml. anat. u. physiol. Vortr. u. Aufsätze. Hrgb. von Gaupp und Nagel, 1909, 1-5.

7. "Während dieser Zeit schreibt das Saitenbild des galvanometers eine horizontale Linie. Vorkammern und Kammern befinden sich in Ruhe, und die durch das Verbindungsbündel fortschreitende Kontraktionswelle ist an und für sich zu schwach um bei der für die Registrierung eines zweckmässigen Elektrokardiograms erforderlichen starken Spannung einen merkbaren Ausschlag des Galvanometers zu erzielen."

8. Tawara: Das Reizleitungssystem des Saugetierherzens, Jena, 1906.

impulse, the Q wave is absent. The R wave represents the spread of the excitation to and the contraction of the right ventricle and more basal lying regions. When S is present, it is an expression of the fact that the left ventricle and more apical regions of the heart soon show a predominant activity over the base and the apex thus becomes relatively electronegative to the base.

The second point of view, developed by Kraus and Nicolai,[8] rests on the well-known division of the ventricular musculature into the papillary system, the circular musculature (Treibwerk) and the outer spiral fibers (Nicolai[9]), the first two being in connection by the so-called intramural fibers. Following the contraction of the auricles the impulse passes over the His bundle and those structures functionally connected with it. The slow conduction in the bundle explains the long interval between the P and R (or S) waves, and no action current of any importance occurs at this time because of the small size of the muscular mass. After this interval the basal portions of the papillary system normally first receive the excitation and as an expression of this the curve rises sharply to form the R wave. The excitation now spreads toward the apex and the R wave ends. This spread of the excitation is largely in a linear direction and explains the large size of the R wave.

The potential differences arising under these circumstances are all in the same direction and are cumulative, while when many muscle masses passing in different directions are the seat of an excitation, the potential differences may to a considerable extent or entirely neutralize one another. The Q wave, when present, is an expression of the fact that the excitation passes in the Purkinje conducting system quite far toward the apex before it reaches the papillary muscles proper. This causes relative apical negativity for a short period. The papillary system includes the papillary muscles proper and the internal longitudinal fibers of the ventricles. Through the auriculo-ventricular conducting system and its ramifications the impulse is distributed to all parts of the papillary system. Normally, the excitation reaches first that part of the papillary system lying toward the base and the true papillary muscles. The base of the ventricle thus shows relative negativity, and the R wave results without a preceding Q wave. The work of Hering[10] tends to show that the true papillary muscles are the first part of the ventricle to enter into contraction. Since these arise toward the apex of the ventricle, they do not form a part of the basal portion of the papillary system and this would seem to be opposed to the view of Kraus and Nicolai. Rehfish[11] notes, however, that

9. Nicolai: Verhandl. d. physiol. Gesellsch. zu. Berlin, Nov. 22, 1907; Zentralbl. f. Physiol., 1907, xxi, 678; Handbuch der Physiologie des Menschen, Hrgb. von Nagel, 1909, i, 805.

10. Hering: Arch. f. d. ges. Physiol., 1909, cxxvi, 225.

11. Rehfish: Deutsch. med. Wchnschr., 1910, xxxvi, 977 and 1035.

the basal portion of the papillary system is more or less firmly fixed by attachments to the aortic cartilage and the auriculoventricular ring, and while this part probably receives the first branches from the His bundle and normally is the first part of the ventricle to receive the excitation, the first part to show movement of sufficient degree to be graphically recorded may well be the true papillary muscles. The basal portions of the papillary system may thus enter first into excitation, but due to the anatomical arrangement, show no visible contraction. Kraus and Nicolai thus conceive of the excitation as spreading out through the His bundle and its ramifications to various parts of the internal longitudinal fibers and papillary muscles of the ventricles. Normally, it affects the basal portions first, and hence the first ventricular wave (R) is directed upward. When the excitation reaches the parts of the papillary system lying more toward the apex of the ventricles, the true papillary muscles receive the impulse at their base and it spreads from base to apex of these muscles, a course opposite in direction to that from base to apex of the ventricle as a whole. This causes a downward-directed wave (Q), a wave stated by Kraus and Nicolai to be absent from the strictly normal electrocardiogram. In such an event, however, the activity of the base soon becomes predominant and the R wave occurs. The R wave is completed when the excitation spreads out from the papillary system through the intramural fibers to the circular fibers (*Treibwerk*) of the ventricles. If the excitation in its spread from the base reaches the apical parts of the papillary system before this occurs, as is usually the case, a short period develops in which there is relative negativity at the apex. This is expressed as the S wave. If, on the other hand, the spread through the intramural fibers occurs before or simultaneously with the excitation reaching the apical parts of the papillary system, the S wave is absent.

It will be seen that considered broadly, the views of Einthoven and of Nicolai in reference to the cause of the Q, R and S waves of the electrocardiogram agree quite closely. No distinction is made in either between the spread of excitation and contraction of the muscle, and it would seem that it is really contraction of the different regions which causes the development of the electrocardiogram. Einthoven even suggested, as we have seen, that the spread of the impulse through the auriculoventricular bundle is associated with a weak contraction. According to both views, this passage through the bundle and conductive system of the heart produces no wave in the electrocardiogram. It is only when the larger muscle masses of the ventricle are affected that any noticeable differences in potential arise. The two views differ mainly as to exactly what muscular masses of the ventricles in their activity produce these differences in potential. Einthoven lays stress particularly on the right ventricular base in the production of the R wave, while Nicolai goes into more detail in reference to the different layers of muscle of the ventricles.

Passing now to the remaining portions of the electrocardiogram, the horizontal part lying between the R (or S) wave, and the T wave, and the T wave itself, both Einthoven and Nicolai explain the former on a general and simultaneous contraction of the musculature of both ventricles, the action currents arising therefrom neutralizing one another so that no difference in potential between base and apex is present. Nicolai lays particular stress on the contraction of the circular fibers (*Treibwerk*). The development of the T wave is explained by Einthoven by the right ventricle (particularly the basal part) remaining in contraction longer than the remainder of the heart, causing the development of a late negativity of the base. This view is founded on the experimental work of Bayliss and Starling,[12] concerning the course of the excitation over the mammalian ventricle. These investigators concluded that in the exposed dog's heart the impulse passed from base to apex, and the indication of terminal basal negativity in the electrocardiogram (recorded by the capillary electrometer from the exposed heart) was to be explained by the base remaining in negativity after the negativity had subsided at the apex and not to a return of the excitation to the base. If under abnormal conditions the contraction ceases in each ventricle simultaneously, as Einthoven supposes to occur in myocardial insufficiency, the T wave is entirely absent. Kraus and Nicolai, on the other hand, explain the T wave as due to a late return of negativity to the base of the heart, a region of the base lying especially around the aorta and pulmonary artery being the last portion of the ventricles to enter into contraction. This view of the course of the impulse was first suggested by Gotch[13] in 1907, and elaborated in more detail in 1909. Gotch conceives the contraction of the ventricle as beginning around the venous orifices, at the base of the ventricle, and spreading to the apex and thence to the arterial bases of the ventricles, following in its course the direction of the primitive cardiac tube. This work will be considered more fully in a detailed discussion as to the course of the T wave later in this paper.

Of other views that have been advanced to explain the normal electrocardiogram, we may next consider the interpretation of Eppinger and Rothberger.[14] As we have seen, both Einthoven and Nicolai explain the electrocardiographic curve as a resultant of the play of antagonistic forces of electric potential between base and apex. Eppinger and Rothberger object to Einthoven's assumption that the relatively weak right ventricle can be regarded as representing, so far as the electrocardiogram is concerned, the cardiac base, and playing the predominant rôle in the production of the normal curve, while the left ventricle with its massive

12. Bayliss and Starling: Internat. Monatsschr. f. Anat. u. Physiol., 1892, ix, 256 and 276.

13. Gotch: Proc. Royal Soc., 1907, 79B, 323; Heart, 1909, i, 235.

14. Eppinger and Rothberger: Wien. klin. Wchnschr., 1909, xxii, 1091.

basal region, is actually regarded as the cardiac apex in this scheme. Eppinger and Rothberger understand Nicolai to regard the R wave as an expression of the spread of the stimulus, to conduction of the impulse in contrast to actual contraction, and cite several facts which they regard as opposed to such an interpretation. They state that if R is referred to conduction alone the interval from P to the end of R, which under these circumstances would represent As-Vs conduction, is actually larger than this conduction period. They find it difficult to understand why the R wave is not always diphasic in such conduction in a linear direction between two points and why the conduction of the excitation produces such a marked effect (R wave) in the terminal connections of the conductive system while it produces no effect in its passage through the bundle and its branches. They believe that the observations of Kahn on the time relation between the R wave and the rise of intraventricular pressure do not support, as they have been supposed to do, Nicolai's interpretation. Kahn, in a series of papers, has studied the time relations between the waves of the electrocardiogram and various features that occur in the cardiac cycle. He found by simultaneous records of the intraventricular pressure, the carotid pulse and the electrocardiogram, that the R wave begins before the pressure in the ventricle rises and is completed during the period of tension, having ended by the time the outflow period begins.[15] Since, according to Nicolai, the R wave is due to the activity of the papillary system, it must occur before that part of the heart musculature which causes a reduction of the internal capacity of the heart becomes active, and this, as we see, Kahn finds to be the case. Similar relations have been found by Kahn to hold between the beginning of the first heart sound and the R wave.[16] Eppinger and Rothberger criticize those facts as applied in support of Nicolai's view, in that they believe that the electrical change actually in all cases precedes the mechanical change to which it corresponds, and call attention to the fact that Kahn's curves show that the P wave of the electrocardiogram also precedes the rise in the pressure curve of the right auricle. Furthermore, they state that the contraction of the musculature must reach a certain point before rise of intraventricular pressure begins. They cite the experiment of Kahn in which he found that in artificial stimulation of the ventricle in vagus standstill the action current began .075 seconds before the rise of intraventricular pressure. Here the contractile substance was directly stimulated and yet the mechanical definitely followed the electrical response. Kahn,[17] in reply to these objections, shows by a series of experiments on the dog's heart that while the electrical latent period of the heart (the time from incidence of stimulus to electrical

15. Kahn: Arch. f. d. ges. Physiol., 1909, cxxvi, 197.
16. Kahn: Arch. f. d. ges. Physiol., 1909, cxxix, 291.
17. Kahn: Arch. f. d. ges. Physiol., 1910, cxxxii, 209.

change) comprises a considerable period of time (.02 to .03 seconds), the difference between the electrical and mechanical response is extremely short, not more than .002 seconds. Kahn concludes from this that the mechanical contraction of that part of the heart, the electrical expression of which goes to form the R wave, must occur not later than .002 of a second after this wave begins. He repeats his original conclusion as to the relation of the R wave to activity in the ventricle and shows that the mechanical activity of the anterior wall of the right ventricle begins after completion of the R wave. The time relations of the rise in pressure in the left ventricle, the first heart sound and the mechanical activity of the wall of the right ventricle to the beginning and length of the R wave of the electrocardiogram confirms the view that the R wave is to be referred to the activity of the papillary system. Kahn further states that he has never committed himself to the view that the R wave is purely a conduction phenomenon, but has merely insisted that the activity of the circular fibers (*Treibwerk*) occurs only after the completion of the R wave and has nothing to do with the production of this wave. Rehfish[11] calls attention to the fact that Eppinger and Rothberger have really misinterpreted Nicolai's statement in reference to the R wave. Nicolai does not state that the R is a pure conduction wave, but that it arises from conduction in and contraction of one of the muscle layers of the heart, namely, the papillary system. It is extremely difficult to obtain from Nicolai's statements the relative parts he regards conduction and contraction to play, if indeed he has in mind any sharp distinction between the two.

Having found serious objections to the two prevalent theories concerning the interpretation of the electrocardiogram, Eppinger and Rothberger present another point of view founded on a long series of experiments in which they attempted to render functionless different layers of the heart muscle by freezing with ethyl chlorid or by the injection of mercuric chlorid or silver nitrate. The results from these experiments lead them to the conclusion that it is not the play of antagonistic electric potentials at the base and apex of the ventricles that produce the electrocardiogram, but that the curve is the resultant of the action currents arising from the longitudinal and circular muscle system of the heart. Activity of the longitudinal musculature causes the galvanometer to give an upstroke (when connected so that the R is directed upward), while activity of the circular fibers neutralizes this or actually produces a downward movement. In other words, the production of the electrocardiogram does not depend on the resultant of electric conditions developed at base and apex of the ventricles from activity of the muscle in these regions, as assumed in the theories of Einthoven and of Kraus and Nicolai, but whether the curve is up or down depends on whether negativity pre-

dominates in the longitudinal or circular fibers of the heart. This conclusion is founded on the following experimental results:

1. Freezing the surface of the ventricles with a spray of ethyl chlorid produces no change in the R wave. This is true for both ventricles and for base and apex. The R wave must arise, therefore, from some deeper structure than the outer longitudinal layer. The T wave becomes smaller or negative on freezing any part of the surface of the left ventricle or the surface of the apex of the right ventricle. Freezing the surface of the base of the right ventricle, on the other hand, increases the T wave (in a positive direction). Section shows that the effect of freezing does not extend at the greatest to a depth of more than 1 millimeter.

2. Injury to the deeper layers of the left ventricle by injection of mercuric chlorid or silver nitrate caused in certain cases increase in the height of R, abolition of S, if present, loss of the level period between R and T, increase of the height and duration of T, and finally fusion of R and T to form a large monophasic upward directed curve. This effect, regarded as typical, was observed in thirteen out of twenty-five cases. In some cases no effect occurred from the injury; in others, there was merely an increase of T and a tendency to fusion with R. The results were the same whether the injections were made into the base or the apex of the ventricle. Injury to the anterior and posterior papillary muscles produced no effect.

3. Injury to the deeper layers of the right ventricle cause in typical cases the appearance, or increase if already present, of the S wave and increase of the T wave. The S and T continue to increase, the R wave becomes reduced and finally disappears and the curve assumes the form characteristic of an extra-systole of the left ventricle. That it is not, however, an extra-systole of the left ventricle is shown by the presence of a P wave. In some cases the R is reduced, the T increased and S is unaffected, but usually the essential change is the appearance or increase of an already present S wave. It is suggested that the different effects observed may be due to differences in the seat of injury, particularly as to whether the auricular or pulmonic regions are affected, but the experiments are not sufficient to demonstrate this.

4. Injury to the interventricular septum causes the same effect as injury to the deep layers of the left ventricle, unless the lesion reaches the muscles lying just beneath the endocardium, when the result is the same as that following injury to the right ventricle.

Eppinger and Rothberger cite the anatomical researches of Krehl and others as showing that while the middle or circular layer of fibers (*Treibwerk*) of the right ventricle is very poorly developed, it forms the greater mass of musculature of the left ventricle. The longitudinal fibers, on the other hand, are well developed in both ventricles. They believe, therefore, that any effect produced by injury to the deeper layers of the

left ventricle can be referred mainly at least, to the circular fibers. Injury to these causes an increase in the whole electrocardiogram in an upward direction, while injury to the right ventricle or internal longitudinal layers of the septum or left ventricle causes the opposite effect. The antagonistic forces at work in the production of the electrocardiogram may thus be regarded as the circular and longitudinal muscular systems. The former in its activity tends to cause the electrocardiographic curve to descend, the latter acts in the opposite direction. The normal electrocardiogram represents the resultant of these two. When one set of fibers is injured, the action of the other preponderates and a corresponding change in the curve occurs.

Eppinger and Rothberger's detailed explanation of the electrocardiogram is as follows: The R wave is an expression of the unopposed action of the internal longitudinal fibers and corresponds therefore to the onset of systole of the ventricles. The remainder of the electrocardiogram is the resultant of the action of two forces. The activity of the circular fibers may predominate for a short time to form an S wave. The level part of the curve between S (or R) and T represents a complete antagonism of the two systems. They make no definite statements in reference to the formation of the T wave. The observation of Einthoven that in man hypertrophy of the left ventricle is frequently associated with a negative R, while in hypertrophy of the right ventricle the R is increased in a positive direction, seemed to support his view that the base of the heart, so far as concerns the production of the electrocardiogram, is represented by the right ventricle and it is the activity of this which normally causes the R wave. Eppinger and Rothberger note that the same fact may be well explained on their interpretation, since in left ventricular hypertrophy the increase is almost entirely in the circular fibers, while in right ventricular hypertrophy it is the longitudinal system which is increased.

In a later paper, Eppinger and Rothberger[18] study the effect on the electrocardiogram of dogs of cutting away the whole of either the right or the left ventricle. Complete removal of the left ventricle causes the normal electrocardiogram to be replaced by a large upward-directed monophasic curve, which persists until stoppage of the heart (usually in about five minutes). The first effect of removal of the right ventricle is a reduction of the R and a great increase in the S wave, but before complete stoppage of the heart the curve assumes a fairly close resemblance to the normal electrocardiogram. The R wave is small, the T very large. It would appear, therefore, that the left ventricle alone can give an approximately normal electrocardiogram, while the right ventricle alone cannot. Since the left ventricle contains both longitudinal and

18. Eppinger and Rothberger: Zentralbl. f. Physiol., 1911, xxiv, 1053.

circular musculature, while the right ventricle contains very few if any circular fibers, these results seem to bear out the interpretation based on their earlier work.

Eppinger and Rothberger thus assign all the waves of the electrocardiogram, more definitely perhaps than either Einthoven or Nicolai, to muscular contraction. The accuracy of their experiments and the value of the conclusions derived from them would seem to depend largely on the exactness of localization of the methods employed for producing loss of function in the different muscle layers. The injury done was apparently determined as far as possible by post-mortem examinations. It must be noted that the experimental results were by no means uniform and many departures from the results they regarded as typical occurred. These may be perhaps explained, as they suggest, by injury to more than one layer. The heart of the frog and tortoise, as shown by Samojloff,[19] Straub,[20] and Gotch,[13] gives an electrocardiogram in every way similar to that of the mammal. We have been unable to find in the literature any full description of the muscular layers of the cold-blooded heart or any study as to the possible differentiation into longitudinal and circular fibers. It is impossible, therefore, to say at present whether the similarity of the electrocardiogram of cold-blooded animals and mammals is opposed to the theory of Eppinger and Rothberger. They suggest that this similarity is best explained on a similar anatomical arrangement of the cardiac musculature in the cold-blooded animal and the mammal.

From results obtained by the action of digitalis on the dog's heart *in situ*, Selenin[21] interprets the electrocardiogram as the resultant of the interference of the electrical waves arising from the right and left ventricles respectively. The ground elements are the diphasic waves of the two ventricles, such as occur in characteristic and unmodified form in extra-systoles of these chambers. An extra-systole of the right ventricle produces a diphasic electrocardiogram in which the first movement (R) is upward, the second (T) downward. The R is large, the T relatively small. An extra systole of the left ventricle, on the other hand, causes a diphasic curve in which the first movement is downward, while the T is positive. The R in this case is smaller than the T. Combining these two curves one may obtain a curve similar to the normal electrocardiogram of the two ventricles. The upward R of the right ventricle more than neutralizes the downward R of the left; therefore the normal R is positive in direction, but smaller than the R of a right ventricular extrasystole. The positive T of the left ventricle is also larger than the negative T of the right ventricle, so the T wave of the normal electrocardiogram is usually in an upward direction. Selenin explains the effect of

19. Samojloff: Arch. f. d. ges. Physiol., 1910, cxxxv, 417.
20. Straub: Ztschr. f. Biol., 1910, liii, 523.
21. Selenin: Arch. f. d. ges. Physiol., 1912, cxliii, 137.

digitalis as causing a preponderance in action of the left ventricle and quotes from the literature in support of the view that digitalis acts mainly on the left ventricle. In the therapeutic stage of action of the drug the P and R are not essentially changed, while the T is increased. As the toxic stages develop the R wave becomes reduced, the T much increased and finally the curve resembles that caused by an extra-systole of the left ventricle. The R almost entirely disappears, it is followed by a large downward-directed wave (S) and a large positive T. The S wave is explained by Selenin by an absence of complete synchronism of the electrical curves of the two ventricles, the S wave really representing the first phase of the diphasic curve of the left ventricle.

Opposed to Selenin's view may be mentioned the observation of Eppinger and Rothberger,[18] that the left ventricle alone may give an approximately normal electrocardiogram, while the right ventricle alone cannot. Eppinger and Rothberger[22] have furthermore shown that when the branch of the His bundle going to either ventricle is cut, the electrocardiogram assumes the form characteristic of an extra-systole of the ventricle still retaining its connection with the bundle. Both ventricles continue to contract and yet the electrocardiogram is profoundly modified. The development of the so-called atypical electrocardiogram characteristic of extra-systoles would seem to depend, therefore, rather on an abnormal entrance of the impulse into the ventricle. Instead of the excitation being conducted to the ventricle over its normal route from the auricle, the His bundle and its branches, it originates at the part of the ventricular muscle stimulated, or in Eppinger and Rothberger's experiments, spreads from the other ventricle. When one ventricle is stimulated, both, of course, contract, and there is no evidence that the one not directly stimulated contracts less strongly than the one stimulated. To support Selenin's view, it would seem necessary to show that the left ventricle contracting alone or the right ventricle contracting alone would give curves, which, on combining, would form the usual electrocardiographic curve as a resultant.

In marked contrast to the preceding views as to the interpretation of the electrocardiogram, is the theory of Hoffmann.[23] From a critical review of the literature, certain observations in man and experimental work on animals, Hoffmann came to the conclusion that the normal electrocardiogram represents two distinct activities in the heart occurring during its systole, namely, conduction of the excitation and contraction of the muscle. Each activity, according to this interpretation, is associated with the development of electrical energy, and so far as the ventricle is concerned, the Q R S complex is caused by the passage of

22. Eppinger and Rothberger: Zentralbl. f. Physiol., 1911, xxiv, 1055; Ztschr. f. klin. Med., 1910, lxx, 1.

23. Hoffmann, A.: Arch. f. d. ges. Physiol., 1910, cxxxiii, 552.

the wave of excitation over the conducting system of the ventricle, while the remaining portion of the ventricular electrocardiogram (level period and T wave) results from the electrical energy liberated by the contracting ventricle. That a possible separation of these two phenomena in the genesis of the electrocardiogram must be considered seems to have been first suggested by Judin.[24] The curve of electrical response of a frog's skeletal muscle (gastrocnemius) shows, according to Judin, a rapid and large wave preceding and a much slower and less intense change accompanying the contraction of the muscle. Judin evidently realized the importance of this observation in reference to the analysis of the electrocardiogram, but so far as we know he has not attempted this in detail. In the article referred to the following statement occurs:

> Dem Aussehen nach erinnert diese Kurve sehr an den Teil des Elektrokardiograms, der sich auf die Ventrikel bezieht. Daraus folgt, das ehe eine Erklärung des Elektrokardiograms gegeben wird, es geboten erscheint, Klarheit in die Frage von den Aktionsströmen des Muskels überhaupt zu bringen, da diese Frage nicht so einfach ist, wie man dies bis jetzt gewöhnlich annimmt.

Hoffmann shows by a review of the literature and by his own experimental work that the R and T waves frequently vary independently of each other, and believes that the R wave cannot be considered as representative of contraction of the ventricular muscle, since it does not, as has been assumed, especially by Einthoven, show any relation in its size to the extent of this contraction. He calls attention to the fact that in the so-called atypical electrocardiogram (electrocardiogram of extrasystoles or ectopic impulse formation[25]) the R wave is much larger than the normal, while in many cases at least the mechanical systole is much weaker than normal. Many observations, on the other hand, indicate that the size of the T wave, frequently, at least, varies directly with the size of contraction.

The T wave is increased during and after muscular work (Einthoven,[4] Müller and Nicolai[26]); it is first increased and then decreased by the action of heart poisons (Kraus and Nicolai[3]), before death it becomes small or disappears (Kraus and Nicolai), and it is small or negative after excessive hemorrhage and in chloroform narcosis (Einthoven[4]). Hoffmann's own experiments speak strongly for the view of direct association between the contraction and the T wave. He recorded the electrocardiogram from frog hearts simultaneously with suspension curves of the ventricle and showed that when the heart is brought to a complete standstill by the application of muscarin, an electrocardiogram is still evident.

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24. Judin: Zentralbl. f. Physiol., 1908, xxii, 365.

25. Hering has introduced the term nomotopic to indicate a normal impulse originating in the normal pacemaker of the sinus region. All impulses originating outside of this area are ectopic.

25. Hering: Arch. f. d. ges. Physiol., 1910, cxxxvi, 466.

26. Muller and Nicolai: Zentralbl. f. Physiol., 1908, xxii, No. 2.

This electrocardiogram from the non-beating heart differs from the normal merely in the absence of a T wave; the R wave is not reduced in size. As the beats return following the removal of the muscarin effect by the application of atropin, the R wave becomes no greater, although the extent of contraction increases rapidly. The T wave, however, reappears, and gradually increases as the size of the beat returns to normal. In the frog's heart during treppe the R wave does not increase as the extent of contractions increase. Application of distilled water to the heart produces weaker and weaker systoles and finally cessation of contraction without decrease in the R wave, but with decrease and disappearance of the T wave. These results show a striking lack of correspondence between the extent of contraction and the R wave and prove that the production of the electrocardiogram is in part unconnected with contraction of the cardiac muscle. The abolition of contraction with maintained conductivity does not entirely abolish the electrocardiogram. The group R (Q, R, S) is to be ascribed, not to contraction of the muscle, but to conduction of the cardiac impulse. Under normal condition the impulse wave, or wave of excitation, is followed by the contraction wave. Under certain experimental conditions, as described above, this does not occur and the change in the electrocardiogram that results is confined solely to the T wave. Hoffmann further notes that in the frog's heart the T wave falls toward the end of systole, and when the length of systole is changed by cooling or warming the heart the T wave separates or approaches R to hold its place always toward the end of systole. The T wave is thus closely associated with contraction and particularly the latter part of the curve. Hoffmann agrees with Einthoven and with Kraus and Nicolai in explaining the level part of the electrocardiographic curve between R and T as due to simultaneous contraction of all parts of the heart and the action currents arising from this neutralizing one another so that no difference in the potential of base and apex occurs. His interpretation of the T wave is essentially that of Einthoven in that it is referred to the cessation of contraction in certain regions of the ventricle while contraction continues in other regions. With reference to each wave of the electrocardiogram the interpretation in detail is as follows: The P wave is the expression of the spread of the impulse over the auricle. The following level part of the curve between P and R represents the contraction of the auricle and the passage of the impulse through the His bundle to the ventricle. The contraction of the auricle is presumably too weak to give any noticeable differences in potential, and hence no auriclar T wave is normally present. The conduction through the His bundle is very slow and this explains why it produces no effect on the electrocardiogram. He cites the work of Grützner, Mackenzie, Kuhe and Biedermann, in showing the absence of electrical change in slowly contracting smooth muscle. The impulse is distributed

first to the papillary muscles. If the parts lying near the apex first receive the impulse from the branches of the bundle, a Q wave occurs. When the excitation reaches the base the R wave occurs. It then rapidly passes to the apex, causing the development of the S wave. By the end of this period the whole musculature of the heart has received the wave of excitation. Now contraction sets in and for a certain period no further change occurs in the electrocardiogram, because all of the heart muscle is active. After a time contraction begins to wane in certain regions and persists undiminished in others and thus gives rise to a difference in potential between base and apex and the T wave is produced.

The essential characteristic of Hoffmann's interpretation and the point in which it differs from all views in reference to the formation of the electrocardiogram is thus the sharp differentiation between the rôle played in its production by conduction of the excitation on the one hand and the contraction of the muscle on the other. As expressed by Hoffmann, the electrocardiogram is to be regarded as a curve of excitation plus the end of a contraction curve.

Considering now in more detail the interpretation of the T wave, the various views that have been more or less definitely expressed may be divided into four groups: (1) The T wave is not really indicative of any potential change arising from activity of the cardiac muscle, but is due to changes in the position of the heart during its contraction, resulting in disturbance of the null point of the galvanometer. 2. The T wave is the result of the contraction of the musculature of certain regions or certain layers of the heart just as the R wave is the expression of the contraction of other regions. 3. The T wave is not a special feature associated with the contraction of musculature from any particular region of the heart, but is a phenomenon associated with contraction of cardiac muscle in general. 4. Some factor or factors enter into its formation other than simple contraction of the muscle.

The first mentioned view has been suggested by Usoff.[27] As a result of contraction of the ventricle the long axis increases and a change of the line of isopotential in relation to the leads to the galvanometer results. Normally, this change in position results from activity of the left ventricle and the T wave is positive. If the right ventricle contracts more strongly than the left the T wave is negative. If the whole heart contracts weakly, as occurs in dilatation, the form change is slight or absent, and the T wave is likewise small or absent. Most authors have attempted to interpret the T wave according to the second mentioned view. Probably the interpretation that has been most widely accepted is that developed by Gotch.[13] In this the T wave is referred to a late contraction of the musculature of the ventricles surrounding the base

27. Usoff: Quoted from Rehfish (Note 11).

of the aorta and pulmonary artery. Gotch attempts to bring the course of the cardiac impulse into relation with the phylogenetic development of the heart from the primitive cardiac tube, and conceives the impulse in the fully developed mammalian organ as entering the auricular end of the ventricle, thence passing to the apex and finally terminating at the arterial base (aortic and pulmonic bases). Bayliss and Starling[12] had previously worked on the course of the impulse over the mammalian ventricle by the method later used by Gotch and had concluded that the late basal negativity (as shown by the T wave of the electrocardiogram) was due, not to return of negativity from the apex to the base, but resulted from the fact that the negativity at the base outlasted that at the apex. They conceived the contraction wave as beginning at the base and passing to and terminating at the apex, while Gotch differentiates between the auricular and arterial bases and supposes the wave of contraction to pass from the first to the apex and thence to the aortic and pulmonic base. Gotch worked on the exposed heart of the tortoise and rabbit with the electrodes placed directly on the surface of the heart and connected with a capillary electrometer. With one electrode in contact with a considerable part of the base of the ventricle, including the muscle lying around the base of the aorta, the other in contact with the apex, he obtained a curve from the tortoise's heart resembling the normal ventricular electrocardiogram with a pronounced T wave. The late negativity of the base (T wave) was not obtained when the basal contact was limited to the lateral regions of the ventricular base, while a localized contact on that part of the base from which the aorta arises gave a curve resembling that obtained when the contact included the basal region as a whole. It seemed clear, therefore, that the portion of the base which is responsible for this late negativity is the region lying at the base of the aorta. The base of the ventricle is thus the seat of two potential changes which occur at different times in ventricular systole, one early, the other late. The second change, that which gives rise to the T wave, is only manifest when the contact of the basal electrode includes that portion of ventricular musculature lying at the root of the aorta. If it is true that the impulse passes as a wave from the auriculoventricular junction to the apex and then returns to the neighborhood of the aorta, the former should show evidence of negativity before the aortic region, and this he found actually to be the case. When one electrode was placed in contact with the lateral parts of the ventricular base and the other with the base of the aorta, the curve obtained was diphasic; the auricular base was first negative and after a period of equipotential, relative negativity developed at the aortic region. The experiments on the exposed heart of the rabbit confirmed this interpretation. Gotch, furthermore, found that in the frog, tortoise and rabbit, an increase in the contraction of the aortic region of the ventricle produced by a rise of blood-pressure is associated with an

increase in the size of the T wave. In the rabbit's heart a weakening of the beat of the ventricle from any cause results in a decrease, or if pronounced, a total disappearance of the T wave. In a strongly-beating rabbit's ventricle shifting the basal electrode away from the aortic (or pulmonic) region results likewise in a reduction of the T wave.

Nicolai, as we have seen, explains the T wave by a return of negativity to the vase and hence agrees with the interpretation first proposed by Gotch. Einthoven, on the other hand, inclines to the conception developed by Bayliss and Starling, that the terminal basal negativity does not represent a return, but a continuation of negativity of this region after it has disappeared at the apex. Eppinger and Rothberger make no very definite statements in reference to the cause of the T wave. They note that since freezing the superficial layer of the ventricular muscle affects only the T wave, while injury to the deeper layers produces none or only a slight effect on this wave, it probably does not arise from activity of the deeper layers. In their description of the effects of injury to the deeper muscles they, however, describe quite marked effects on the T wave.

The third point of view mentioned above, namely, that the T wave is not to be referred to any special region or layer of musculature, but is an essential feature accompanying the contraction of cardiac muscle in general, is the central idea in Hoffmann's interpretation of the electrocardiogram. Hoffmann, as we have seen, differentiates sharply between the electrical effect produced by conduction, on the one hand, and contraction on the other. The first is represented in the ventricular electrocardiogram by the group R (Q, R, S), the second by T. Early in systole, when the whole cardiac muscle is in contraction, no T wave normally develops because the various action currents produced neutralize one another so that no difference in potential between base and apex is present. Such difference in potential only arises when some portion of the heart (normally the apical regions) begin to pass out of contraction, while others (normally the basal regions) remain strongly contracted. While thus it is really one particular region of the heart, the ventricular base, which is mainly concerned in the production of the T wave, by this point of view as expressed, any contracting cardiac muscle, no matter from what region of the heart, should give a T wave if the change in potential thereby induced is unopposed by simultaneous changes developed in other regions of the heart.

Finally, the view that some other factor besides simple contraction of heart muscle plays a rôle in the formation of the T wave has been suggested by Samojloff and by Straub. Samojloff,[19] working on the frog's heart, came to the conclusion that the T wave is composed of two components, one representing conduction of the excitation, the other contraction of the muscle. He found in extra-systoles of the frog's ventricle

that while the direction of the R wave changed, depending on whether the extra-systole arose from base or apex stimulation, that the T wave always retained the direction present in the normal beat. However, the size of the T wave varied in these two cases. When the T wave in an extra-systole is in the same direction as the R, it is smaller than in a normal beat, while when the T is in opposite direction to the R, it is larger than the normal. This can be explained if the T wave is regarded as representing the second part of a diphasic curve of conduction, plus a contraction curve, in which the latter element always predominates. The part of the T representing conduction is always opposite to the R, representing as it does, the second part of a diphasic change. When the second component of the T (representing contraction) is opposite in direction to this, these two subtract from each other and the T is small. When they are both in the same direction the two components are added and the T wave is larger than normal. It will be noted that in each case the second component of the T (that representing contraction) predominates. Straub[20] places the T wave at the beginning of diastole in the frog's heart and suggests that it may be in some way connected with assimilatory processes in the muscle. He showed that warming the ventricle increases its size (in a positive direction), while cooling causes it to become small or negative.

The T wave, as has been noted by most writers, is by far the most variable feature of the electrocardiogram. While in the normal curve from man it is nearly always in the same direction as the R wave, in the frog, tortoise and in mammals used in experimental work a downward-directed (negative) T wave is not at all uncommon in an apparently normal heart beat. Many observations have been made in an attempt to determine the factor or factors that underlie the variations in size of the T wave and the majority perhaps point to the conclusion that a close correspondence exists between the extent of ventricular contraction and the size of this wave. The work of Hoffmann in this connection and the literature he cites has already been referred to. Rehfish,[28] in an extensive as determined by orthodiagraphic methods. The highest positive T waves comes essentially to this conclusion. In an analysis of 350 clinical cases the size of the T wave was compared with the arterial blood-pressure as measured by the v. Recklinghausen tonometer and the size of the heart as determined by orthodiographic methods. The highest positive T waves were present in cases of moderate blood-pressure (111 to 130 mm. systolic pressure), and in which there was no great enlargement of the heart, but in which the *x*-ray examination showed particularly strong heart movement. The most pronounced examples of this type were cases of well-developed hypertrophy with no evidence of broken compensation, espe-

28. Rehfish: Ztschr. f. exper. Pathol. u. Therap., 1911, ix, 716.

cially well marked in cases of pure cardiac neuroses. In pronounced heart weakness or in dilatation and in very small hearts with low blood-pressure, the contractions of the heart, as shown by the fluoroscope, are small, and these are always associated with a small T wave. In greatly enlarged hearts with very high blood-pressure (180 to 250 mm. systolic) the T wave is small or negative in the majority of cases. The R wave shows a tendency to increase in size with increase in blood-pressure and increase in size of heart, but the change is not so marked as occurs in the case of the T wave. Pribram and Kahn[29] conclude from a study of over 300 pathological cases that while variations in the size of the T wave in apparently similar cases is quite common, in general T is strongly positive in forcibly contracting hearts, while it is small or absent in very weak hearts. While they find that frequently the R wave is modified in right and left ventricular hypertrophy in the way described by Einthoven, many exceptions occur. Samojloff[19] found that in the electrocardiogram of the frog's heart the first systole following the compensatory pause of an extra-systole produced by stimulation of the ventricle ("post extra-systolic systole") shows a larger T than normal, while the R wave is unchanged in size. The T wave of the second normal systole following an extra-systole is, however, smaller than that of succeeding systoles. Langendorff[30] and Bottazzi[31] have shown that the first post extra-systolic systole is larger, the second smaller, than the average systole. In the electrocardiogram these changes in size of systole are marked solely by changes in size of the T wave. Moreover, in the extra-systole itself the T wave is smaller than normal and this difference is more pronounced the earlier the extra-systole follows a normal systole. As is well known, the earlier an extrasystole falls in the preceding cycle the smaller the contraction. The size of the extra-systolic contraction is thus directly connected with the size of the T wave. That the T wave frequently varies independently of the R and seems to depend as to degree of its development largely on the extent of contraction of the heart, is further indicated by studies on the action of certain poisons on the heart and on the influence of the extrinsic cardiac nerves.

The action of drugs of the digitalis series has been studied by Nicolai and Simons,[32] by Straub,[33] and more recently by Selenin.[21] The last-named investigator worked on dogs with hearts *in situ* and found that in the stage of therapeutic action of digitalis the P and R waves were not essentially changed from the normal, while the T wave was increased in size. Nicolai and Simons describe in man an increase in size of the T

29. Pribram and Kahn: Deutsch. Arch. f. klin. Med., 1910, xcix, 479.
30. Langendorff: Arch. f. d. ges. Physiol., 1898, lxx, 473.
31. Botazzi: Zentralbl. f. Physiol., 1896, x, 401.
32. Nicolai and Simons: Med. Klin., 1909, v.
33. Straub: Ztschr. f. Biol., 1909, liii, 106.

wave without essential change in the R as a result of therapeutic doses of digitalis. Straub describes similar effects from strophanthin in cats and rabbits at the beginning of the toxic stage of action. Further action causes a negative T. Epinephrin (adrenalin) causes the T to become large and negative. The increase of the T is the characteristic effect of the action of digitalis on the frog's heart, according to Straub.[20] Hering,[34] in studying the *pulsus alternans* produced by the intravenous injection of glyoxylic acid, found that the most common change in the electrocardiogram produced by the ventricular alternation is in the T wave; the R wave is never alone affected and is always less changed than the T. In a previous paper, Hering[35] had shown that the essential feature in the alternation produced by glyoxylic acid in the mammal's heart is not a hyposystole (diminished contraction) of the whole ventricle, but a partial asystole. Certain parts of the ventricle do not enter into contraction at all in the alternating small beats. The view that *pulsus alternans* is a hyposystole seems to have been first suggested by Gaskell,[36] and to have been confirmed for the frog's heart by Trendelenburg,[37] and by Muskens.[38] Hering could find no relation between the portion of the ventricle affected and the change in the T wave and concludes that the T wave is produced by every part of the musculature which may be in activity toward the end of systole and is not to be referred to any special region of the ventricles. Kahn and Starkenstein[39] confirm Hering in that they find in *pulsus alternans* produced by glyoxylic acid that the T wave varies considerably in size in the large and small beats, while the R wave is little affected.

The effect on the electrocardiogram of section and stimulation of the extrinsic cardiac nerves has been studied in detail by Rothberger and Winterberg.[40] Increased accelerator influence as a result of vagus section causes increase in P. R is unchanged or smaller and T is much increased. Stimulation of the right stellate ganglion with vagi intact causes a similar change. Stimulation of the left stellate ganglion causes P to become small; R becomes diphasic with pronounced S wave; T usually becomes strongly negative. Increase of vagal effect by section of accelerators causes P and T to undergo marked decrease, while R is increased. They conclude that the effect of increased accelerator influence is the result of a localized strengthening of the contraction, a "partial hypersystole." In reference to the anatomical distribution of the right and left accelerator fibers they believe that stimulation of the left accelerator

34. Hering: Ztschr. f. exper. Pathol. u. Therap., 1909, vii, 363.
35. Hering: München. med. Wchnschr., 1908, lv, 1417.
36. Gaskell: Philosoph. Tr., 1882, clxxiii, 993.
37. Trendelenburg: Arch. f. (Anat. u.) Physiol., 1903, p. 271.
38. Muskens: Jour. Physiol., 1907, xxxvi, 104.
39. Kahn and Starkenstein: Arch. f. d. ges. Physiol., 1910, cxxxiii, 579.
40. Rothberger and Winterberg: Arch. f. d. ges. Physiol., 1910, cxxxv, 506.

causes negativity of the T wave due to increased strength of contraction of the left ventricle, while increase of the T in a positive direction from stimulation of the right accelerator is due to increased contraction of the right ventricle.

The rôle that different parts of the ventricle play in the genesis of the T wave has been studied in an interesting series of experiments by Henle.[41] Hering and Biedermann had shown that as a result of the application of a constant electric current to the frog's heart the region of the ventricle under the anode remains uncontracted while the current is passing. If the current is very strong the effect may spread to the entire ventricle, but by using a current of moderate strength a well localized effect may be obtained. For a short time following the cessation of a current which has been passing for some time, the region around the anode contracts more strongly in each systole than the remaining parts of the heart, while the region surrounding the cathode shows diminished activity. These effects likewise involve larger areas the stronger the current employed. If the current is not too strong it is possible to obtain a localized region which contracts to a less or to a greater degree than the remaining ventricular muscle. Henle applied this method to the study of the effects produced by these localized regions of depressed or augmented activity on the electrocardiogram from the heart of frogs and mammals (dogs). Since the passage of a current through the heart would affect the electrocardiogram, he utilized the effects produced on the heart which follow the withdrawal of the current, namely, an augmentation surrounding the anodal and a depression surrounding the cathodal region. One electrode, which can be made either anodal or cathodal, is placed on the heart; the other serves as an indifferent electrode connected with some portion of the body surface. By the use of a commutator a galvanic current is passed through the heart for a period of fifteen to twenty seconds and then by reversal of the key connection is made with the galvanometer and the electrocardiogram obtained from the surface of the heart (base and apex of the ventricle) for the next few beats. With the anode on the base or the cathode on the apex of the heart, the effect on the electrocardiogram in the next few beats following the cessation of the current was an increase in size of the T wave over the normal. The T wave is thus increased in a positive direction when the base contracts stronger or the apex weaker than normal. With the anode on the apex or the cathode on the base the T wave is small; in the first two or three beats following the withdrawal of the current it may be negative. The R wave is practically unaffected. As a result of the current probably the activity of only the superficial layer of the heart muscle is affected, and since this affects only the T wave it is suggested

41. Henle: Ztschr. f. Biol., 1911, lv, 295.

by Henle that the R and T arise from different layers of muscle. The fact that change in the extent of contraction of the musculature at the apex as well as at the base of the ventricle affect the T wave, proves that at the time of occurrence of this wave the apical musculature as well as the basal musculature is in functional activity and that both play a part in its production. This is, of course, opposed to the explanation of the T wave upheld by Gotch and by Kraus and Nicolai.

The production of the T wave, according to the majority of writers, is closely connected with the activity of some special layer or region of ventricular muscle. Only Hoffmann (and perhaps Judin) have suggested that it is representative of contraction of cardiac musculature, irrespective of position. In relation to this conception of great importance is the observation by Straub[42] of the presence of a T wave from the auricle of the isolated frog's heart. After complete cessation of the contraction of the ventricle with continued contraction of the auricles, Straub obtained a diphasic curve followed by a monophasic curve; the latter resembling the T wave of the ventricle. This observation on the frog's heart has been confirmed by Eiger[43] and more recently by Hering.[44] Hering also finds some indication for the presence of a T wave in a curve obtained from the auricles of a dog beating *in situ* after the ventricles have been cut away. He states, however, that such a conclusion can only be arrived at with great reservation and that further work is required to establish an auricular T wave in the electrocardiogram from mammals and from man.

Before closing a review of the recent literature on the electrocardiogram, reference may be made to the interesting series of observations of Paul Hoffmann[45] on the electrocardiogram of the invertebrates. Three types of electrocardiograms, according to this work, are to be recognized. The first type is characterized by a series of oscillations, varying in number from two or three to twenty or more and extending throughout the period of contraction. This type is characteristic of the heart of certain arthropods, namely, *Limulus*, *Maia* and *Astacus*. The heart is evidently in tetanic contraction and the curve is simply a number of action currents rapidly following in succession, each corresponding to an excitation received from the cardiac center in the intrinsic cardiac nervous system. No T wave is present, probably due to the rapidly recurring contractions going to make up the tetanus. The second type of electrocardiogram is characteristic of certain hearts which show a peristaltic contraction, a representative of which is found in the gastropod, *Aplysia*. The electrocardiogram is a simple diphasic curve. Finally

42. Straub: Ztschr. f. Biol., 1910, liii, 499.
43. Eiger: Extr. de Bull. de l'Acad. des Sciences de Cracovia, July, 1911.
44. Hering: Arch. f. d. ges. Physiol., 1912, cxliv, 1.
45. Hoffmann, P.: Arch. f. (Anat. u.) Physiol., 1911, p. 135.

the third type is the electrocardiogram characteristic of all the higher animals, found among certain of the higher invertebrates (certain cephalopods) and all the vertebrates. The differences of the electrocardiogram in these different animals are therefore associated with distinct differences in the physiological peculiarities of the heart, and the type of electrocardiogram of the higher animals, including man, is characteristic of the type of activity that is peculiar to the heart of the higher animals.

THE RELATION OF THE ELECTROCARDIOGRAM TO OTHER EVENTS IN THE CARDIAC CYCLE

The work of Kahn[15, 16, 17] in this connection has already been referred to. Similar observations have been made by Weiss and Joachim[46] and by Bull.[47] There is general agreement that the R wave precedes by a few hundredths of a second (.03 to .06) the onset of ventricular systole as shown by the rise of intraventricular pressure and the first heart sound. The relation of the electrocardiogram to the venous pulse has been studied by Rautenberg.[48] While he agrees that the onset of the R wave precedes the beginning of ventricular systole and finds that the position of the c wave on the venous pulse confirms this view, he concludes that the R wave is nevertheless to be referred to and is representative of the first part of ventricular systole. He assumes that the P wave is to be referred exclusively to contraction of the auricles and its beginning must correspond to the onset of auricular systole. Determining on his curves the distance that the auricular wave of the venous pulse follows the P wave of the electrocardiogram, he applies this correction to the relation between the c wave of the venous pulse (onset of ventricular systole) and the R wave of the electrocardiogram. When this correction is made, he finds that the beginning of the R wave falls in all cases exactly with the beginning of the c wave, and concludes that both represent the same process in the heart, namely, the beginning of ventricular systole. The R wave thus represents the contraction of the ventricular muscles as a whole and not merely of the papillary system, since the contraction of the latter causes no rise in intraventricular pressure. The reason that it occurs in point of time before the cardiac muscle contracts is to be referred to the latent period of the heart muscle. Considering for the time that Rautenberg's assumption that the beginning of the P wave is representative in all cases of the onset of auricular systole, and that the correction as applied to the relation between the R and c waves is correct, the work of Kahn[17] on the relation between mechanical movement and electric response which we have already referred to in some detail, is entirely opposed to Rautenberg's interpretation. As will be discussed

46. Weiss and Joachim: Ztschr. f. klin. Med., 1911, lxxiii, 240.
47. Bull. Quart. Jour. Exper. Physiol., 1911, iv, 288.
48. Rautenberg: Berl. klin. Wchnschr., 1910, lxvii, 2190.

later in this paper, we believe we have strong evidence to indicate that the onset of the P wave in by no means all cases corresponds to the onset of auricular systole. The observation of Einthoven[3] and others, that the P-R interval is of different length in different leads to the galvanometer from the same individual, indicates that either the P wave in relation to auricular systole or the R wave in relation to ventricular systole, or both, undergo variation.

We have studied the relation of mechanical systole of the heart to the electrocardiogram, with especial reference to the P-R interval, in man and in the dog. Comparative measurements were made of the a-c interval on the venous pulse and the P-R interval of the electrocardiogram in simultaneous records of the two from fifteen normal men. These show, contrary to the findings of Rautenberg, that the P-R interval on the electrocardiogram does not correspond in the majority of cases with the a-c interval on the venous pulse. Usually the a-c interval is somewhat longer than the P-R interval, so that if P is made coincident with a, c does not fall at the beginning of R, but towards the end of this wave. In a few cases the two intervals are of approximately the same length and in several cycles in these records the a-c interval is definitely shorter than the P-R interval. The probable interpretation of these differences will be discussed later. Our results thus indicate that the P-R interval is not in most cases a measure of the As-Vs interval. The opposite conclusion of Rautenberg seems to have been derived from records which showed a relation other than the usual one. A more interesting point in reference to the interpretation of the electrocardiogram shown by these records is the duration of systole. As is well known, only on certain phlebograms is the end of systole sharply marked by the separation between the t and d waves (Bard[49]). In records from seven of the fifteen individuals, the end of systole was evident and these without exception showed that the length of systole, as measured by the c-d interval on the venous pulse, corresponds to an interval on the electrocardiographic curve beginning near or at the end of R to the end of T. If the end of the T wave is representative of termination of the contraction of the ventricular muscle, as is generally recognized to be true, it is evident that the onset of mechanical systole is represented, not by the beginning of the R wave, but by a point at or near the termination of this wave. Figures 1 and 2 are simultaneous records of the jugular pulse and electrocardiogram in man and show the features discussed above. Figure 3 is a record from a dog and gives a comparison of the a-c interval on the jugular pulse and the P-R interval of the electrocardiogram in the same cycle. The venous pulse was recorded by a sound introduced into the right external jugular vein according to the method used by

49. Bard: Jour. de physiol. et de pathol. gén., 1906, viii, 454.

Fredericq.[50] The electrocardiogram in all these records is from Lead II of Einthoven (right anterior and left posterior extremities). In several experiments on dogs we have compared the P-R interval with the As-Vs interval as recorded by suspension curves of the right auricle and right ventricle. These have led to the same conclusion. Certain abnormal conditions of the heart which may cause a wide variation between the two will be discussed later. Finally, in simultaneous records of the venous pulse, electrocardiograms and apex beat in four normal men, the venous pulse has been corrected for transmission by comparison with the cardiographic curve and this correction applied to its relation to the electrocardiogram. When this correction is made, the time from the onset of the P wave to the a wave of the venous pulse is less than the time from the onset of the R wave to the c wave of the venous pulse. If the beginning of P is to be referred to the onset of auricular systole, the beginning of R does not correspond to the onset of ventricular systole. From these observations the following conclusions may be drawn:

1. Auricular systole plus auriculo-ventricular conduction time is not accurately represented on the electrocardiogram by the interval from the beginning of the P wave to the beginning of the R wave (P-R interval). In the majority of cases the As-Vs interval corresponds to an interval from the beginning of P to some point on the descending limb of R or the end of this wave.

2. The period of systole of the ventricle, or the time from the rise of intraventricular pressure, as marked by the c wave of the venous pulse, to the closure of the semilunar valves, as marked by the d wave of the venous pulse, is represented in the electrocardiogram by the interval from the end of R to the end of T.

From the work of Keith and Flack,[51] Wybauw,[52] Lewis and Oppenheimer,[53] Brandenburg and Hoffmann,[54] Ganter and Zahn[55] and others, we have strong evidence that the cardiac impulse in the mammalian heart arises in a region of tissue representing embryological remains of the primitive sinus and lying in the adult organ along the sulcus terminalis of the right auricle at its junction with the superior vena cava. The excitation spreads from this region to the auricles and thence to the ventricles by the auriculoventricular bundle. The question at once arises whether or not the activity of the so-called sinus region is represented in the electrocardiogram. Is the P wave representative entirely of activity of the auricles, or does the cardiac impulse before reaching the

50. Fredericq: Arch. internat. de physiol., 1907, v, 1.
51. Keith and Flack: Jour. Anat. and Physiol., 1907, xli, 172.
52. Wybauw: Arch. internat. de Physiol., 1910, x, 78.
53. Lewis, Oppenheimer and Oppenheimer: Heart, 1911, ii, 147.
54. Brandenburg and Hoffmann: Med. Klin., 1912, viii, 16.
55. Ganter and Zahn: Zentralbl. f. Physiol., 1912, xxv, 782.

auricular tissue proper play a part in the production of the electrocardiographic curve? We have recently studied in a series of experiments on the dog's heart *in situ* the conduction of the excitation from the sinus region, the results from which will form the subject of another paper, but certain facts bearing on the present problem may be discussed here. The Keith-Flack node manifests development of a negative potential in the dog's heart from 0.025 to 0.03 second before the body of the right auricle. This result was obtained by measuring the time from the occurrence of negativity in these two regions in relation to mechanical systole of the auricle. One electrode was placed on the node, another on the auricle and these connected in turn through the galvanometer to an indifferent electrode on the left hind leg of the animal, the systole of the right auricle being recorded at the same time by suspension. There is, therefore, a slight delay in the passage of the impulse from the node to the auricle, a sino-auricular interval which amounts, under normal conditions, to from 1/5 to 1/3 the auriculoventricular interval in the same animal. By comparing in the same experiments the relation of the onset of the P wave of the electrocardiogram to mechanical systole of the auricle, it was possible to determine whether the negativity in the sinus region formed the first part of the P wave or whether the wave is to be referred exclusively to excitation in the auricle. An example will make this clear. In one experiment an electrode placed on the sinus region and connected with an indifferent electrode on the left hind leg, showed that the first negativity developed at the sinus preceded the onset of mechanical systole of the auricle by 0.08 second. The lower part of the body of the right auricle developed negativity 0.05 second before auricular systole. The P wave of the electrocardiogram (leads from right anterior and left posterior extremities) finally began 0.07 second before auricular systole. The first two of these determinations were made in the same record by means of a key used to connect the electrodes on the sinus and auricle in turn with the galvanometer and indifferent electrode. The relation of the P wave to auricular systole was determined from a record immediately following the proceeding. It is evident from the data in this experiment that the wave of negativity passed from the sinus node to the body of the auricle within 0.03 second and that the P wave of the electrocardiogram was in part made up of this negativity, while still in the sinus region and in part after it had spread to the auricles. Our experiments have also demonstrated that there is no restricted path of tissue by which the impulse spreads from the sinus to the auricle. Such conduction occurs by diffuse paths, and this is probably the explanation as to why the manifestation of sinus activity and of auricular activity on the electrocardiogram are fused to form a single wave (P), and do not form two separate waves. A splitting of the P wave has been described by Hering[46] and others. Hering suggested that

the first part represented activity of the sinus, the second part activity of the auricles. We have seen a similar division into two waves in an experiment in which the sinus region was partially isolated from the auricle by cuts through the cardiac tissue, and this suggests that a splitting of the P wave may indicate unusual difficulty in conduction from the sinus node to the auricle. The point we wish to emphasize here, however, is that the P wave of the electrocardiogram, in the majority of cases at least, is a composite of the spread of the excitation in the sinus region and in the auricles. The onset of this wave does not, as a rule, correspond to the development of activity in the auricles, but is coincident with or more frequently begins a short time after the excitation becomes evident in the sinus region. No separate wave occurs normally in the electrocardiogram of mammals indicating activity of the sinus because the region is connected with the auricles by many and diffuse paths and there is a relatively small delay in the passage of the excitation to the auricle. In the cold-blooded heart, the sinus, although present as a separate chamber, the contraction of which is separated by a considerable interval from that of the auricles, does not as a rule produce any effect in the electrocardiogram, probably because its activity is too small. Using a very sensitive thread in the galvanometer we have obtained evidence of a wave preceding the P wave of the electrocardiogram in the tortoise from leads from the body tissues of the animals and perfectly clear and definite results when the leads were from the exposed heart, one from the sinus, the other from the ventricle. An example is given in Figure 4. There is a wave resulting from a sinus activity, followed by the usual P, R and T waves. That leads from the surface of the mammalian heart fail to show under normal conditions any evidence of a sinus wave separate from that of the wave produced by activity in the auricle would seem then to be the essential difference between the electrocardiogram of the cold-blooded heart and the mammalian heart and to be the expression of the difference in the two cases of the physiological relation between the sinus and auricles. In the example given above, the data are such as to lead to the conclusion that the first onset of negativity in the sinus region does not give rise to the P wave. In the majority of cases this is true, and while only in exceptional cases does the P wave begin first when the activity reaches the auricle, usually the very first development of negativity in the sinus does not affect the electrocardiogram. Probably if the galvanometer in all cases were sufficiently delicate, the onset of the P wave would correspond always to initial negativity of the sinus.

Having thus to consider the P wave as made up in practically all cases in part by activity in the sinus region, and the extent to which this enters varying in different cases, we have at once an evident factor to account, in part at least, for differences between the P-R interval and the

interval from auricular systole to ventricular systole (As-Vs interval), as measured by mechanical means. If one explains the electrocardiogram on the hypothesis that it represents two separate processes occurring in the heart muscle during its activity, namely, conduction of the excitation and contraction of the muscle, the P and R wave are to be regarded as representing the former process in the auricles and ventricles, respectively. If the P and R waves are then not manifestations of contraction of the auricular and ventricular muscle, but of the spread of the wave of excitation, another factor may be considered which may act to change the P-R interval independently of the As-Vs interval. It is conceivable that the period from the time of entrance of the excitation into the muscle to the contraction may undergo variations and may be different in the case of the auricle and ventricle. The latent period of mammalian heart muscle to direct stimulation varies markedly at different times in the cardiac cycle (Hirschfelder and Eyster[56]). A third factor which may perhaps alter the P-R interval without changing the As-Vs interval is variation in the conductivity from the sinus region to the auricle. By application of nicotin to the sinus and basal portions of the right auricle we have found that the P-R interval may become actually twice as long as the As-Vs interval, as measured by suspension of the right auricle and right ventricle. The change in the P-R interval in this case was shown to be due entirely to an earlier occurrence of the P wave before mechanical auricular systole. An example of these experiments may be given. Before application of the nicotin the P-R interval averaged 0.10 second, the As-Vs interval 0.13 second. These were measured from the same cycles. The P wave preceded auricular systole by .055 second. Following the application of 50 per cent. nicotin the P-R interval averaged 0.13 second, the As-Vs interval 0.06 second; P preceded auricular systole 0.13 second.

Whether these may or may not be the main factors involved in causing variations in the P-R interval independently of the As-Vs interval, the fact is evident that it can be shown experimentally that the P-R interval is not an accurate measure for this period, and that the two may show independent variation. As we have seen, usually the P-R interval is a few hundredths of a second shorter than the As-Vs period. The occurrence of the P wave before the excitation enters the auricle would tend to make it larger, yet normally the reverse is true. While perhaps a definite answer cannot be given as to the cause of this, it seems to us that it may be well explained on the following grounds: When the excitation reaches the auricle it affects at once muscles the contraction of which cause decrease in the internal capacity of this chamber. This is not true in the case of the ventricle. The excitation

56. Hirschfelder and Eyster: Am. Jour. Physiol., 1907, xviii, 222.

passes down the His bundle into the papillary system and is thence distributed to the remainder of the ventricular musculature. It is not until the circular fibers of the ventricle are in activity that any decrease in the interval capacity of the ventricle occurs and a rise of intraventricular pressure results. The work of Hering[10] has demonstrated that the papillary muscles contract at least .02 to .03 second before the main mass of ventricular muscle.

The fact that the length of systole is expressed on the electrocardiogram, not by the distance from the beginning of R, but from the end of R to the end of T, would seem again to point to the conclusion that the R wave can have nothing to do with the contraction of any musculature which tends to decrease the size of the ventricle. In strong support of this is the experimental proof of Kahn,[17] to which we have previously referred, that the muscle which, by its activity, produces the R wave must contract following this wave a much shorter period of time than does the mechanical systole of the ventricle.

THE RELATION OF THE LINE OF ISOPOTENTIAL TO THE FORMATION OF THE ELECTROCARDIOGRAM

As has been pointed out, particularly by Kraus and Nicolai,[3] the electrocardiogram is the expression of the algebraic sum of many electric potential differences conducted away from the heart by its interior and exterior surfaces to the peripheral tissues. The whole heart serves as an indifferent conductor for potential differences arising at any point within the organ and the actual potential at any given point at any time is due to the activity in this region modified by activity occurring at this time in all other regions. We may suppose to exist, as was first described by Waller,[1] in reference to any two leads from the extremities, a line or equator of equipotential passing through the heart between base and apex. A preponderance of negative potential above this line (basal portions of heart) causes the movement of the galvanometer connected with the two hands in such a way as to indicate relative negativity of the electrode connected with the right hand. In leads from a hand and foot, the hand assumes this relative negativity. A preponderance of negativity below this line causes movement of the galvanometer in the opposite direction.

We have attempted to afford experimental evidence for this assumption by artificially producing a condition of negativity in various regions of the heart and determining the effect produced on the galvanometer connected in the usual way with two leads from the extremities. Dead dogs were used. The animal was placed in a large sheet-iron tank, the bottom of which was covered with saline solution to a depth of several centimeters. Leads to the galvanometer were made from the right

anterior and left posterior extremities. Six non-polarizable electrodes were placed on various regions of the heart. These were connected with a switch with six contact points by means of which any one of the electrodes could be placed in a circuit with a battery and a large sheet-iron plate on the bottom of the tank containing the animal. By this means a current could be sent through the animal, entering by a large area through the skin of the back and leaving by a much smaller area on the surface of the heart. While this condition probably resembles little the actual condition present in the beating heart in which a potential difference arises between two points from activity of the muscle, we were able to demonstrate the fact that a difference of potential arising under the conditions of our experiment affect the galvanometer connected with the two limbs differently, depending on what region of the heart shows this change in potential. The relation between different points on the heart may thus be compared and a line of isopotential demonstrated under the conditions present. Change in potential along this line causes no movement of the galvanometer. A negative charge above this line causes the galvanometer to move in a direction indicating relative negativity of the electrode connected with the anterior limb. A negative charge below this line causes the galvanometer to move in the opposite direction. The actual position of the line of equipotential in our experiments was an arbitrary one and could be shifted by varying the position and extent of contact of the animal with the salt solution in the tank. The relation of other parts of the heart to the region transversed by this line, however, remained quite constant. The position of the six electrodes was as follows:

1. (a) Region of the sinus (Keith-Flack) node, (b) or body of right auricle.
2. Region of the auriculoventricular (Tawara) node at the base of the interauricular septum.
3. Auriculoventricular bundle near bifurcation.
4. Left ventricular apex.
5. Right ventricular base.
6. Aortic base of left ventricle.

The results from the three experiments of this character may be summarized as follows: When the line of isopotential passed along the region of the ventricles, a movement of the galvanometer indicating negativity of the anterior electrode (right fore limb) occurred when the current was passed through the electrodes on the sinus, the right auricle, the A-V bundle and the region of the Tawara nodes. The extent of movement was in the order named. The two ventricular bases showed movement in the same direction as the above and to about an equal degree. No marked difference was obtained, but in two of the three

experiments the movement was slightly greater for the aortic base than for the base of the right ventricle. Measurements from a record may be given as follows:

Sinus	—13
Intraventricular septum	—12
A-V bundle	—10
Left ventricular apex	+ 4
Right ventricular base	—10
Aortic base of left ventricle	—10

The figures refer to the movement of the thread in millimeters. The minus sign indicates movement showing relative negativity of the anterior electrode. The plus sign indicates negativity of the posterior electrode. By shifting the contact of the back of the animal with the salt solution in this experiment, a movement of the thread indicating relative negativity of the anterior electrode occurred in all cases. The relation between the extent of movement in each case remained, however, without change.

While we realize that the application of any results drawn from the above experiments to the normal electrocardiogram must be applied with all due reservation, we believe the fact that the basal regions of the ventricle show similar relations to the leads from the limbs as do the supraventricular regions of the heart, and particularly the absence of any marked difference between the base of the right and left ventricles, is at least suggestive. It would seem to be opposed to the views of Einthoven[5] and Selenin[21] that the two ventricles in their activity represent the opposing influences in the production of the normal electrocardiogram and would tend to lay stress on the difference between base and apex in this connection. The fact that a line of isopotential can be obtained experimentally under the conditions described, and that there is general agreement in the curves obtained with those representing potential changes in the normal beating heart, as for example, the fact that activity of the right auricle produces always in the beating heart relative negativity of the anterior electrode while activity of the ventricular apex affects movement in the electrocardiogram in the opposite direction, seem to us to offer support to the view that normally there is such a region of isopotential between base and apex and it is the balance of potential on the two sides of this which determines whether the electrocardiographic curve moves in one direction or the other. The simplest explanation of why the P wave, for example, is monophasic in the electrocardiogram from the extremities while it may be diphasic in direct leads from the auricle, is that all of the activity producing it is above the line of isopotential. Whether or not the T wave is positive or negative in direction may also be well explained by the resultant of activity above and below this line. In a T wave directed in the same

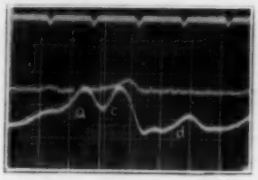

Fig. 1.

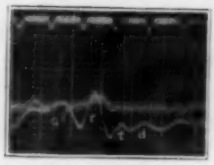

Fig. 2.

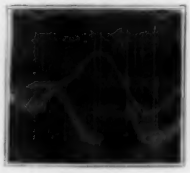

Fig. 3.

Fig. 1.—Electrocardiogram (Lead II) and venous pulse from man. Time record in 1/5 sec. To show comparative lengths of the P-R and a-c intervals, and the R-T and c-d intervals.

Fig. 2.—Similar to Figure 1.

Fig. 3.—Electrocardiogram (Lead II) and venous pulse from a dog, to compare the length of the P-R and a-c intervals.

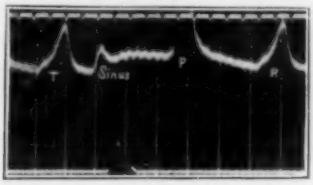

Fig. 4.

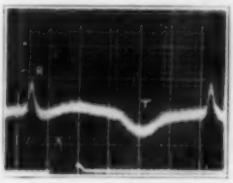

Fig. 5.

Fig. 4.—Electrocardiogram from superficial leads from the exposed tortoise heart, to show the wave arising from sinus activity. The leads to the galvanometer were from the sinus and ventricular apex. The lowest line signals the mechanical systole of the sinus. The electrocardiographic record shows a sinus wave followed by a P and R wave. The time record is in 1/5 second.

Fig. 5.—Electrocardiographic curve obtained from the exposed tortoise heart (leads from right auricle and ventricular apex) in which the ventricle had ceased beating as a result of the application of a second Stannius ligature. Time in 1/5 sec. intervals. The lowest line signals the auricular systole.

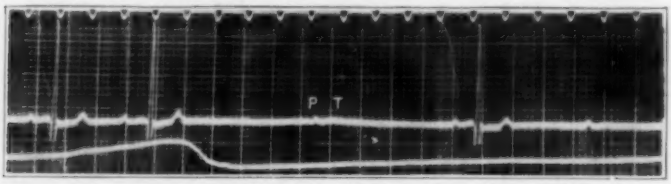

Fig. 6.

Fig. 6.—Electrocardiogram (Lead II) from a dog, showing heart-block as a result of a toxic dose of morphin. The blocked cycles show a small wave following the P which is interpreted as an auricular T wave.

Fig. 7.

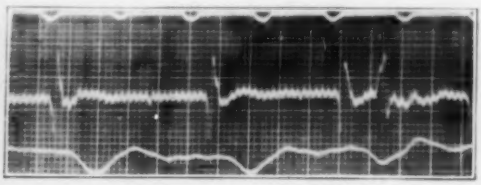

Fig. 8.

Fig. 7.—Electrocardiogram (Lead II) from a dog, showing heart-block as a result of pressure applied to the region of the auriculoventricular node. The blocked cycle shows an auricular T. The lowest line records the mechanical systole of the right auricle.

Fig. 8.—Curve from dog's heart *in situ* with leads to the galvanometer from the exposed right auricle and from the left posterior leg. Heart-block from vagus stimulation, showing the auricular T. The lowest line records the mechanical systole of the right auricle.

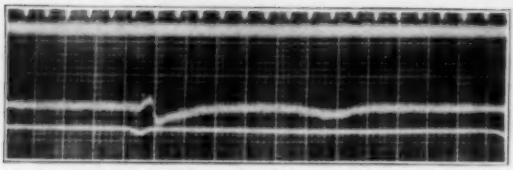

Fig. 9.—Action current from a longitudinal strip of ventricular muscle from the tortoise ventricle not including any of the region of the aortic base. Shows a diphasic R followed by a T wave accompanying the contraction resulting from mechanical stimulation. The lowest line records the contraction.

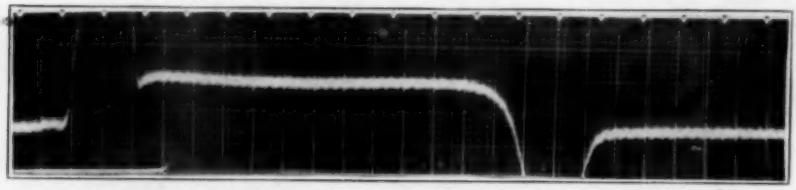

Fig. 10.—Action current from a strip of ventricular muscle cut from the apical region of the tortoise ventricle. Monophasic R followed by T. The lowest line signals the contraction of the strip.

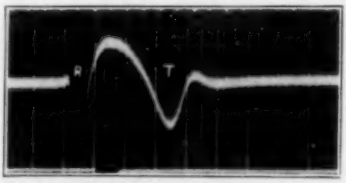

Fig. 11.—Similar to Figure 10. T in same direction as first movement of R.

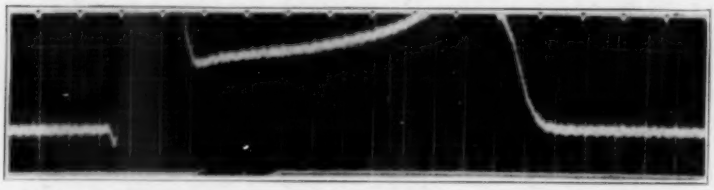

Fig. 12.—Action current from strip cut crosswise from the mid-region of a tortoise ventricle and stimulated mechanically. The contraction of the strip is signaled by the lowest line of the record.

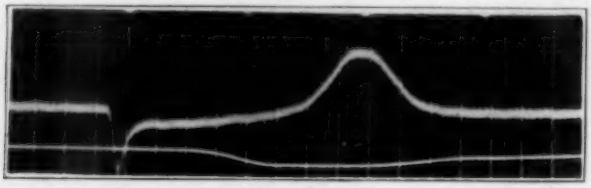

Fig. 13.—Action current from the ventricle of a cat after removal of the basal regions. Mechanical stimulation. The lowest line of the record shows the duration of contraction.

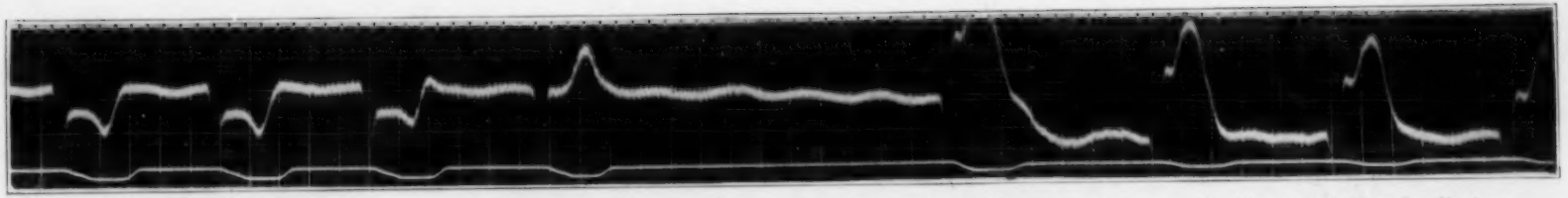

Fig. 14.—Showing the effect on the T wave of the auricle of vagus stimulation. Tortoise heart; ventricle quiescent as a result of a second Stannius ligature. Leads from right auricle and basal part of quiescent ventricle. The period of vagus stimulation is indicated by the small rapid oscillations of the galvanometer thread produced by the escape of the stimulating current. The lowest line records the mechanical systole.

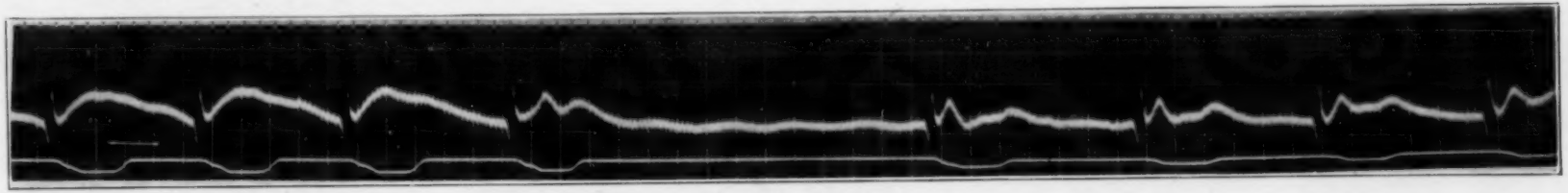

Fig. 15.—Similar to Figure 14.

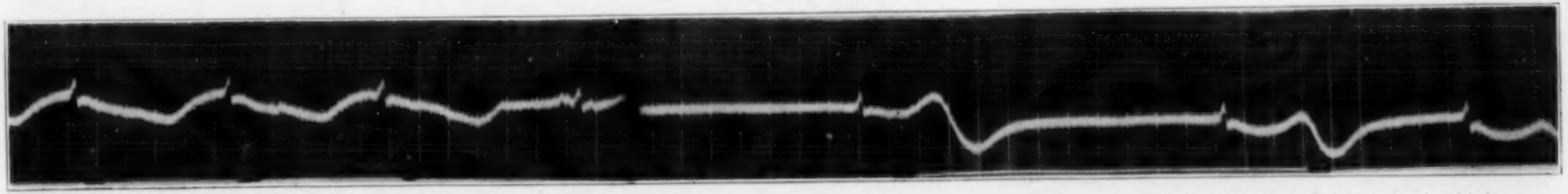

Fig. 16.—Similar to preceding. Shows the transition stages of the results of vagus stimulation. The record was stopped for a short period in order to obtain recovery stages following the stimulation. The mechanical systole of the auricle is signaled by the lowest line.

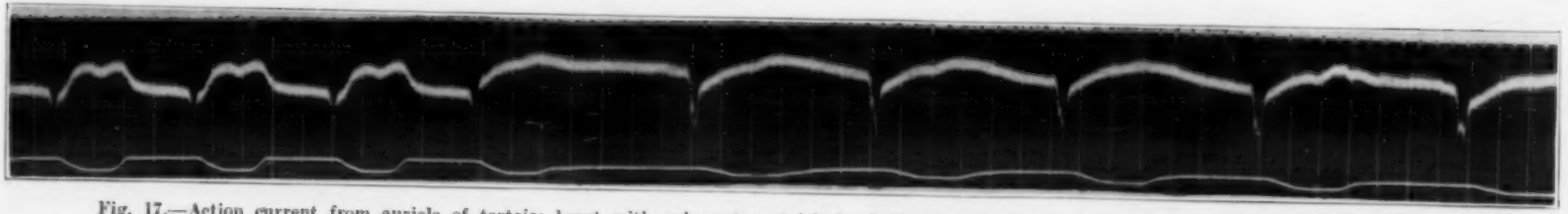

Fig. 17.—Action current from auricle of tortoise heart with quiescent ventricle in similar preparation to those of the preceding figures. Shows the effect on the auricular T wave of the application of Ringer's fluid at 4 C. The lowest line records the mechanical systole of the auricle.

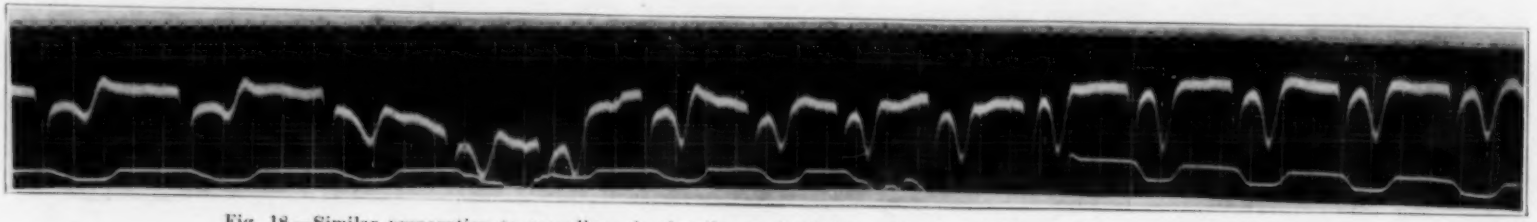

Fig. 18.—Similar preparation to preceding, showing the result of the application of Ringer's fluid at 42 C. to the heart.

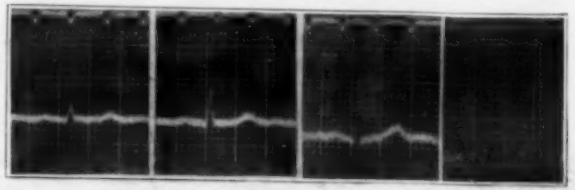

Fig. 19.—Four electrocardiograms from the same individual taken over a short space of time with thread of different sensitivity. Lead II.

direction as the P, the predominant activity producing it would be in the ventricular bases, while a T in the opposite direction (so-called negative T wave) would seem to depend on excess of activity in the more apically lying ventricular musculature.

THE INTERPRETATION OF THE T WAVE

The various views that have been advanced to explain the T wave have been described. Our own observations support the view of Hoffmann,[22] in so far as this investigator separates between conduction and contraction in cardiac muscle and refers the T wave to the latter.

We have succeeded in demonstrating the presence of a wave resembling in all characteristics the T wave of the electrocardiogram in (1) the auricle of the cold-blooded heart; (2) the auricle of the mammalian heart; (3) the ventricle of the tortoise's heart after destruction of the musculature around the aortic ring; (4) in simple strips from the tortoise's ventricle, from the apical as well as the basal regions, and (5) from strips cut from the mammalian ventricle. When isolated, and changes in other regions prevented from modifying the curve obtained, all of these show as the result of stimulation and a sufficiently sensitive galvanometer two sharply marked electrical changes — first, a rapid monophasic or diphasic curve, followed by a much slower and more prolonged variation. Figure 5 shows the curve obtained from a tortoise's heart with a second Stannius ligature and quiescent ventricle. The heart was *in situ* and the leads to the galvanometer from the right auricle and ventricle. Each auricular beat shows a rapid electrical change followed by a much slower variation in the opposite direction. The time of auricular contraction is marked by a signal (lowest curve of record). In this particular case the second wave is opposite in direction to the first and might be considered as the second part of a diphasic variation. Opposed to this interpretation is the great delay between the two movements, the fact that the first wave resembles an R, the second a T wave, and that frequently the two movements are in the same direction, or the first may be clearly diphasic and this be followed after a time by a slower monophasic change. Figure 6 shows a T wave of the auricle of a dog in partial auriculoventricular block resulting from a toxic dose of morphin.[57] The electrocardiogram was obtained in the usual way from the right anterior and left posterior extremities. Following the P wave of the blocked cycle there is a small but definite prolonged variation in the same direction. Figure 7 shows a small T wave in the auricle in partial auriculoventricular block in the dog's heart arising from pressure on the region of the auriculoventricular node. The position of the auricular T is marked by an X. The lowest line of this record is a

57. Eyster and Meek: Heart, 1912, iv, 59.

suspension curve of the right auricle, the downstroke representing systole. The heart was *in situ*, the chest opened and the leads to the galvanometer from the right anterior and left posterior extremities. This wave occurred regularly in all cycles where the conduction was blocked. It is evident in the unblocked cycles that the development of this wave would be impossible, since it would be entirely obscured by the ventricular R wave. Figure 8 is a curve obtained from a dog with heart *in situ* and leads from exposed right auricle and left posterior leg. As a result of stimulation of the vagus the first two cycles show only auricular contractions. The lowest line of the record records these contractions. Each beat of the auricle causes a rapid diphasic curve followed by a slow monophasic curve. In the third cycle the auricular contraction is followed by a systole of the ventricle and a diphasic ventricular curve obscures the formation of the auricular T wave.[58] Pronounced T waves have been obtained from the tortoise's ventricle after complete destruction of the aortic regions and from strips of ventricular muscle cut from various regions of the ventricle. Figure 9 is a curve obtained from a longitudinal strip of ventricular muscle not including any of the region of the aortic base. Mechanical stimulation of one end of the strip resulted in a contraction with the production of a diphasic curve followed after a considerable interval by a slow monophasic curve. Figure 10 is a curve from a strip cut from the apex of a tortoise's ventricle and stimulated mechanically. The galvanometer was very sensitive and shows movements that carried the shadow off the record. There is a monophasic curve followed after a pause of over one and a half seconds by another large monophasic change in the opposite direction. Figure 11 is from a similar strip and shows a rapid mono- or partially diphasic curve with a slower change in the same direction as the original movement of the galvanometer thread. Figure 12 is a curve from a strip cut crosswise from the mid-region of a tortoise's ventricle and stimulated mechanically. There is an initial electrical change followed by a slower movement in the same direction.

To explain satisfactorily these curves as a result of contraction alone would seem to be impossible. In Figure 12, for example, it would be necessary on such an assumption to suppose that the contraction began at the end stimulated and spread out from this region, and that after a relatively long period of time there occurred a second contraction following the same course. If one assumes, however, that the two electrical waves actually represent two different processes, conduction of the excitation and contraction of the muscle, the second following the first after a certain interval, the interpretation is not difficult.

58. Fig. 13, Plate 17 of Samojloff's paper[59] shows a well developed auricular T wave in auriculoventricular block from vagus stimulation. The author makes no reference to this in the text.

Figure 13 is a curve obtained from mechanical stimulation of the ventricle of a cat, removed from the body and suspended. The auricles and whole basal region of the ventricle, including the region of the origin of the aorta and pulmonary artery, were cut away. The lowest line of the record records the contraction. It will be seen that this begins after the first electrical wave is completed and ends coincidently with the termination of the second electrical wave. The relation of the contraction to the two waves is strikingly like the relation of the R and T waves of the normal electrocardiogram to mechanical systole of the ventricles as discussed in a preceding section of this paper.

That we are actually dealing, in all cases considered above, with a wave similar in all essential details to the T wave of the electrocardiogram is indicated on several grounds. In the first place it is difficult or impossible to interpret the curves in any other way. In the second place, the wave which we believe to be the T wave in the ventricular strips shows a peculiarity in reference to its form which was first noted by Einthoven as characteristic of the T wave of the electrocardiogram. The T wave is characterized by a slow rise and a relatively rapid fall and in this is unique among physiological curves. Finally, we have performed a series of experiments on the supposed auricular T wave of the tortoise's heart which show it to undergo variations in size and direction under certain experimental conditions which have been shown to be characteristic of the T wave of the electrocardiogram of the ventricle. These include the effect of vagus stimulation and of heat and cold applied directly to the heart. Samojloff[19] has analyzed the influence of vagus stimulation on the electrocardiogram of the frog's heart as follows: During vagus stimulation the T wave of the ventricle shows a decrease in the upward direction (when the leads are such that R is positive in direction), or changes from a positive to a negative T. The R wave is not affected, but the R-T interval is shortened. Following the stimulation the T gradually returns to its normal direction and size and the R-T interval becomes normal. During the vagus stimulation the T does not change in direction abruptly as a rule, but the first effect is usually that along with the decrease of the T, a movement in the opposite direction begins preceding the original purely positive wave. At this time the T is really diphasic with the first movement in the opposite direction to the original wave. Finally, the last part of the diphasic curve disappears and the T is represented by a monophasic curve in the opposite direction to the original wave. This also explains why the R-T interval is shortened. The reverse process occurs during the return to normal after the stimulation.

Figure 14 shows that similar changes occur in the T wave of the auricle as a result of vagus stimulation as described by Samojloff for the T wave of the ventricle. The record is from a tortoise's heart in

which the ventricle is quiescent as a result of a second Stannius ligature. The leads to the galvanometer were from the right auricle and basal part of the quiescent ventricle and are connected in such a way that the P wave (which for convenience of description may be designated here as the "R" wave of the auricle) is directed downward. The lowest line is the contraction curve of the auricle recorded by suspension. It is evident here, as in previous records, that the contraction begins after the "R" is completed and ends near the end of T. Stimulation of the right vagus was begun toward the end of the second cycle shown on the record, and its duration is indicated by the small oscillations it produces in the thread of the galvanometer. The first two cycles are before vagus stimulation and show an auricular T wave in the same direction as the P (auricular "R"). In the third cycle the T has already begun to manifest change in direction as a result of vagus stimulation, while the "R" wave is unchanged. In the fourth cycle the change is complete. Following the stimulation, the first few beats show a still further development of this change with a marked shortening of the R-T interval. The condition tends to pass off toward the end of the record. Figure 15 shows a similar result to a less marked degree. The conditions here were the same as in the preceding experiment. The "R" wave is diphasic. The T wave before stimulation is a long slow change opposite in direction to the initial change of the "R." Vagus stimulation, the onset and duration of which is shown by the effect on the thread, decreases the T wave slightly in height and apparently splits it into two parts. The "R" is unchanged. Figure 16 shows the transition stages in the change of the auricular T wave as described by Samojloff for the ventricular T. The conditions were the same as in preceding experiments. Before stimulation, the T wave is directed downward and is a long, slow wave, resembling the T of Figure 15. The recording apparatus was stopped for a short time following the vagus stimulation and during the recovery a diphasic T wave with the initial change in the opposite direction to the original T is apparent. The onset of auricular systole in this record is marked by a signal.

Straub[20] has shown that in the frog warming the heart increased the size of the T wave of the ventricle, while cooling the ventricle causes the T wave to become small or negative. We have found that the T wave of the auricle of the tortoise behaves similarly. Figure 17 shows the effect of application of cold Ringer's fluid (4 C.) to the exposed heart of the tortoise. The ventricle was quiescent as a result of a second Stannius ligature. The leads to the galvanometer were from the right auricle near the tip and the base of the quiescent ventricle. The cold saline solution was applied after the third cycle. The effect is a practically complete abolition of the T wave of the auricle. The P wave is also reduced and shows division. Figure 18 is from a similar preparation

and shows the effect of application of Ringer's solution at 42 C. The T wave increases in size from 10 to 20 millimeters. The effect in each case passed off shortly after the records shown and the condition returned to normal.

In a recent paper,[59] in which we have attempted to trace experimentally the course of the excitation over the tortoise heart, we have given a number of facts which we believe incompatible with Gotch's interpretation of the T wave. The excitation in its spread over the heart was traced by means of the action current recorded by leads from various points on the surface of the heart. The experiments are fully described in this paper and only certain points will be referred to here. In leads to the galvanometer from the aortic base and apex of the ventricle, the negativity in the former preceded in all of eighteen experiments. In eleven of these the T wave was in the same direction as the initial movement of the R wave, in seven it was in the opposite direction. It is difficult to understand on Gotch's view how the T wave can ever be opposite to the R in this lead, since such a feature would imply, on his interpretation, terminal activity of the apex. In the experiments of this series eighteen different leads from various regions of the heart were compared. In twelve of these leads the results were uniform in a great majority of the experiments as to the direction of the initial movement in the R wave. In some of these cases the R was monophasic, in others diphasic, and this was true not only in different leads in the same heart, but the same lead in different hearts. Marked variability was present, however, in the direction of the T wave. The variations in one lead, the aortic base and apex, are given above. While in most leads there was a distinct majority of cases in which the T wave had a certain direction in relation to the direction of the R, and thus a more or less typical curve for any given lead, exceptions were always present and in some cases the T was in the opposite or in the same direction as the R in about an equal number of cases. Certain other examples of this besides the aortic base-apex lead may be given. In eighteen left anterior base and apex leads the R wave in all cases was in a direction indicating primary negativity of the base. The T wave was in the same direction in twelve cases, in the opposite direction in six. In the lead from the left and right posterior ventricular bases, the former showed initial negativity in eighteen of twenty-three cases. In these eighteen cases the T was in the same direction in ten cases; in the opposite direction in eight. Many other examples could be given, but these are sufficient to illustrate the fact that the T wave in the same leads from the heart may vary in direction in reference to the R to a marked degree. Two hearts which show in the various leads exactly the same sequence of activity in the

59. Meek and Eyster: Am. Jour. Physiol., 1912, xxxi, 31.

different regions, as indicated by the direction of the R waves, may thus have T waves in the opposite direction. If the T wave as well as the R is to be referred to conduction of the excitation we should have to assume, therefore, marked differences in the spread of the excitation in these two cases. In each case the initial course of the impulse as shown by the same direction of the R waves is the same, but if the T wave is involved in the interpretation the final course of the impulse would be exactly opposite. That the initial course should be so constant, while the terminal course shows such marked variations, would seem very improbable. A much more satisfactory explanation, and one more in accord with other known facts, is to assume that the R and T waves represent different phenomena. The former we believe to be representatives of the spread of the excitation, the latter of the active contraction of the muscle. Since the spread of the excitation in the normal heart is probably a constant factor, the R wave in the same leads from different hearts is practically constant in direction. The direction that the T wave assumes in relation to the R is probably determined by the region of the ventricle that manifests the greatest activity in the contraction or that remains contracted for the longest time. Many known experimental influences may modify the extent of contraction in different regions of the ventricle and such modifications probably occur as a result of the action of various uncontrolled factors in many experiments, particularly when the heart is exposed. Whether this be the true explanation or not, the facts stated offer other examples of variations in the direction and character of the T wave with unchanged R wave and offer additional support to the view that these two waves represent essentially different activities in the heart.

The R wave with leads from two points on the exposed heart, or from two ends of a strip of cardiac muscle, may be either monophasic or diphasic. The same lead in two hearts may give a monophasic R in one case and a diphasic R in the other. The curve obtained in the passage of an excitation over a muscle between two electrodes is usually diphasic, but as is well known, monophasic curves are not infrequent. The apparent explanation in the latter case is that the activity associated with the excitation, while spreading to the second electrode, remains preponderant at the region of the first electrode.

A further point may be noted in reference to our experiments on the exposed heart of the tortoise, namely, that the size of the T wave is usually greatest when one or both of the electrodes were on a part of the heart which enters into strong contraction. The smallest T waves were obtained from leads from the auriculoventricular ring where contraction is very small.

We shall not attempt to give in this paper a review of the rather large literature concerned with the question as to whether conduction and contraction are to be regarded as different phenomena in skeletal muscle. The studies of v. Brücke[60] and Noyons,[61] concerning the action of asphyxia on the relation between the action current and extent of contraction would seem to show that the two may vary independently. The mere fact that a nerve manifests conduction and no contraction would suggest the possibility of the independence of the two processes in muscle. The experiments of Hoffmann on the heart in which contraction was abolished by drugs and the R wave unaffected, have been referred to in detail. Trendelenburg,[62] in a recent study of the relation between the refractory phase of the heart and the action current, finds that one may be made to vary independently of the other. He finds also in standstill from muscarin, that the action current of the heart may be very little affected.

The normal electrocardiogram is usually described as showing a level phase between the end of the R and the onset of the T wave, explained, as we have seen, by most writers as due to simultaneous contraction of the whole musculature of the ventricle and the numerous action currents arising neutralizing one another so as to give no demonstrable difference in potential. This explanation has been objected to by certain writers (Rautenberg, Rehfish) on the theoretical ground that such a perfect antagonism could not be expected in all cases. We have become convinced by a study of our electrocardiographic curves, as well as those published by others, that the normal electrocardiogram is not characterized by a period of equal potential between base and apex at this time. In the great majority of records, especially when the galvanometer is somewhat more sensitive than that ordinarily used in recording electrocardiograms from man, the curve shows a gradual rise following the end of R (or S). When the T is well developed the curve may proceed upward at once on the completion of the R without any evidence whatever of a horizontal period. Records obtained from the same individual with successive increase in the sensitiveness of the galvanometer, show that the apparently horizontal portion of the electrocardiogram disappears with increase in delicacy (Fig. 19). The condition, therefore, which gives rise to the T wave is actually present very soon after the termination of the R wave. It may reach its full development rapidly and the crest of T be reached without interruption, or at first it may be present in relatively small degree and develop more rapidly toward the end of systole.

60. v. Brucke: Arch. f. d. ges. Physiol., 1908, cxxiv, 215.
61. Noyons: Onderzoeck physiol. Lab. Utrecht v Ruks., 1909, x, 215.
62. Trendelenburg: Arch. f. die ges. Physiol., 1912, cxliv, 39.

THE INTERPRETATION OF THE NORMAL ELECTROCARDIOGRAM

Our own experiments and a review of the literature has led us to agree essentially with the interpretation of Hoffmann, that the normal electrocardiogram is the expression of two different processes occurring in the heart muscle during its activity, namely, the spread of the excitation and the mechanical shortening of the muscle. The facts which speak for such a view may be stated briefly. In the nerve where conduction alone is present, a single monophasic or diphasic electric response is obtained. In skeletal muscle this rapid electrical change is followed by a slower and more prolonged monophasic variation. These two electrical manifestations, present also in cardiac muscle from all parts of the ventricle as well as from the auricle, may vary independently, one may be abolished and the other persist, or either may change in size independently of the other.

The electrocardiogram as obtained in the usual way with leads from the extremities is an expression of those two processes. In the usual electrocardiogram there is no electrical expression of the contraction of the auricle, while the electrical expression of the ventricular contraction is evident (T wave). This is due to the fact that the ventricle contracts much more strongly, but especially that the electric wave resulting from this contraction is not obscured by any process of conduction occurring at this time. The auricles during their contraction as well as the ventricle develop electrical energy, but the movement of the galvanometer that is produced is ordinarily obscured by the wave (R) associated with conduction of the excitation in the ventricle. When such conduction is prevented (auriculoventricular heart block, isolated auricles), the contraction of the auricles causes a definite electrical change (T wave of the auricle) to be evident on the electrocardiogram.

The P wave of the electrocardiogram is to be referred to passage of the excitation from the point of origin in the sinus region over the auricle. In the cold-blooded heart, where the activity of the sinus and of the auricle are separated by a relatively long interval, the P wave is preceded, when the galvanometer is sufficiently sensitive, by a wave representing the passage of the excitation over the sinus. In the mammalian heart, on the other hand, where the sinus is closely incorporated with the right auricle, while its activity precedes that of the auricle by only a very short period (.03 second), even with the most sensitive galvanometer no evidence is obtained of a separate activity preceding the P wave. There may be, however, a division of the P wave when the conduction is delayed between the sinus and auricle and the conditions approach that present in the cold-blooded heart. Under normal conditions in the mammalian heart, however, the P wave is due in part to sinus activity, as is shown by comparative measurement between the onset of sinus activity and auricular contraction, on the one hand, and

of the P wave and auricular contraction on the other hand. Whether or not the passage of the impulse through the auriculoventricular conductive system, the His bundle and its main branches to the right and left ventricle enters into the formation of the R wave, is not clear from our present knowledge. Against this is the presence of an R wave in the cold-blooded heart, where the auriculoventricular conduction system is less specialized and in conduction between any parts of the ventricle or over a strip of heart muscle. It is also extremely difficult to explain the Q wave on this assumption. While this wave may perhaps not be a feature of the strictly normal electrocardiogram, it is present in many cases, and must be explained when present. Hoffmann does not commit himself to the exact portion of the conducting system which is responsible for the R wave. Nicolai has attempted to explain, however, in detail, as we have seen, how the various normal modifications in the R group (Q, R, S) may occur by variations in the distribution of the impulse to the ventricle. It would seem that more experimental knowledge is necessary before we will be in a position to state exactly what anatomical structures are involved in this interpretation. We believe the evidence is sufficient at present to refer the R group mainly or exclusively to the process of conduction of the excitation. The question as to the exact structures involved we believe to be capable of experimental test and we hope to return to this in a later paper.

The T wave of the ventricle in the normal electrocardiogram we believe to be the expression of preponderance of contraction on one side of the line of equipotential. Whether this wave is directed in the same or the opposite direction to the R wave depends on a balance between the action current produced by the contracting muscle on each side of this line. The direction of the T wave and its size in either direction would seem to depend on (1) the position of the line of equipotential in relation to any given lead, (2) the extent of contraction of the ventricular muscle as a whole and (3) the relative degree of contraction in the basal and apical regions of the ventricle. The T wave is essentially a manifestation of contraction and occurs as a result of contraction of cardiac muscle from all parts of the heart. Its size and direction in the electrocardiogram is, however, modified by the factors named.

BOOK REVIEW

A Text Book of Pathology for Students of Medicine. By J. George Adami, M.A., M.D., F.R.S., and John McCrae, M.D., M.R.C.P. (Lond.), illustrated with 304 engravings and 11 colored plates. Lea & Febiger, Philadelphia, Pa., 1912.

The task of preparing this book in one volume, which was evidently set on the shoulders of the authors by the publishers, is no small one. Dr. Adami and Dr. McCrae deserve great credit for having constructed out of the large text-book a single volume of so much merit. For it is not merely a condensation of the large treatise, but a text-book intended for a somewhat different purpose and, therefore, devised accordingly. An attempt has been made to present the student with the fundamental framework on which our ideas of diseases are based, and in doing this time and space have been devoted rather to a consideration of the general pathological processes and abnormal disturbances of physiology, than to minute and accurate descriptions of gross anatomical and microscopical lesions.

It follows, therefore, that the five chapters on "General Pathology" lead one almost half way through the volume of some 700 pages. The plan adhered to in the treatment of this section follows fairly closely that of the large volume. There has been, however, selection as well as condensation, and though in places the text would seem to be a little difficult for the beginner to follow, the concise descriptions are in the main clear, and to the point.

It seems to us, too, that the treatment of the special pathology has been very deftly arranged. Manifestly, it is impossible in a book of this size to furnish comprehensive descriptions of anatomical lesions, and, indeed, a good illustration is often worth pages of text. Such descriptions have therefore been relegated to a comparatively unimportant position, though of course mention is at least made of all departures from the anatomical normal. An excellent feature of this second part is a concise discussion of the pathological physiology of the various systemic diseases, which, after all, in such a treatise furnishes the student with a readable and fundamentally correct introduction to the subject. Thus in the chapter on special pathology of the blood and cardiovascular system about fifty pages are devoted broadly to pathological physiology, and thirty to morbid anatomy.

The introductory discussions to the chapters on diseases of the respiratory system, nervous system and urinary tract, though not so extensive, are also good, and to be greatly commended. The same method might have been carried out with perhaps more telling effect in the chapter on diseases of the digestive system, and a similar discussion, and short chapter devoted to diseases of the glands of internal secretion, would have added much to this second part.

One need not expect, therefore, to find in this book more than an outlined description of morbid processes *per se*, but he will discover a discussion, in framework, of active pathological processes, which serves as an excellent and readable introduction to the study of active diseases. Aside from the fairly numerous halftones, there are two or three colored plates of really great beauty.